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 DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
 MEDICAL DEVICES ADVISORY COMMITTEE

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GENERAL AND PLASTIC SURGERY DEVICES PANEL

+ + +

April 27, 2011
 8:00 a.m.

Holiday Inn Gaithersburg
 2 Montgomery Village Avenue
 Gaithersburg, Maryland

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KAREN E. BURKE, M.D., Ph.D.	Voting Member
SUSAN HALABI, Ph.D.	Voting Member
A. MARILYN LEITCH, M.D.	Voting Member
MARY H. McGRATH, M.D., M.P.H.	Voting Member
DELORA L. MOUNT, M.D.	Voting Member
MICHAEL J. MILLER, M.D.	Temporary Voting Member
AMY E. NEWBURGER, M.D.	Temporary Voting Member
MICHAEL G. HALPIN	Industry Representative
KRISTINE R. MATTIVI, M.S.	Consumer Representative
E. PAIGE BROWN STRONG	Patient Representative
MARGARET McCABE-JANICKI, B.S.	Designated Federal Officer

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MEETING

(8:00 a.m.)

DR. GALANDIUK: I would like to call this meeting of the General and Plastic Surgery Devices Panel to order.

I am Dr. Susan Galandiuk, the Acting Chairperson of this Panel. I'm a general surgeon specializing in the field of colon and rectal surgery. I'm a Professor of Surgery and the Director of the Price Institute of Surgical Research at the University of Louisville in Kentucky.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote upon information related to the pre-market approval application for Restylane, sponsored by Medicis Aesthetics, Inc. Restylane is currently approved for the mid-to-deep dermal implantation for the correction to moderate and severe facial wrinkles and folds, such as nasolabial folds. The Sponsor is requesting an expanded indication to include the use of Restylane for submucosal implantation for lip augmentation.

Before we begin, I would like to ask our distinguished Panel Members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. We'll

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begin at my far right with Mr. Melkerson.

MR. MELKERSON: I'm Mark Melkerson, Director for the Division of Surgical, Orthopedic, and Restorative Devices with the FDA's Office of Device Evaluation.

DR. HALABI: I'm Susan Halabi, a biostatistician, associate professor at Duke University.

DR. MILLER: I'm Michael Miller. I'm Professor of Plastic Surgery at the Ohio State University.

DR. NEWBURGER: I'm Amy Newburger, a dermatologist in private practice in Scarsdale, New York, and I teach at St. Luke's-Roosevelt Hospital.

DR. LEITCH: I'm Marilyn Leitch. I'm a surgical oncologist at UT Southwestern in Dallas.

DR. MOUNT: I'm Delora Mount. I'm Associate Professor of Surgery and Pediatrics and craniofacial surgeon at the University of Wisconsin in Madison.

MS. McCABE-JANICKI: Hi, I'm Margaret McCabe-Janicki. I'm the Designated Federal Officer for this Panel.

DR. BURKE: I'm Dr. Karen Burke. I'm a private practice dermatologist in New York, and I'm associated with the Department of Dermatology at Mt. Sinai Medical Center in New York.

DR. McGRATH: I'm Mary McGrath. I'm a plastic surgeon and

Professor of Surgery at the University of California, San Francisco.

MS. BROWN STRONG: I'm Paige Brown Strong, and I'm the Patient Representative for this Panel.

MS. MATTIVI: I'm Kris Mattivi. I'm the Consumer Representative for this Panel. I'm the manager of analytic services at the Colorado Quality Improvement Organization, the Colorado Foundation for Medical Care.

MR. HALPIN: Hi, I'm Mike Halpin. I'm the Industry Representative today, and I work for Genzyme Corporation as Vice President of Regulatory Affairs.

DR. GALANDIUK: Thank you. If you haven't already done so, please sign in at the attendance sheet by the tables near the doors.

Ms. McCabe-Janicki, the Designated Federal Officer for the General and Plastic Surgery Devices Panel, will make some introductory remarks.

MS. McCABE-JANICKI: Good morning. I will now read the Conflict of Interest and Deputization to Temporary Voting Member Statements.

The Conflict of Interest Statement and Appointment of Temporary Voting Member Statement.

The Food and Drug Administration (FDA) is convening today's meeting of the General and Plastic Surgery Devices Panel of the Medical Devices

Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees (SGEs) or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S. Code Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act (FD&C Act) are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with the Federal ethics and conflict of interest laws. Under 18 U.S. Code Section 208, Congress has authorized FDA to grant waivers to special Government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees have been screened for potential financial conflicts of interest of their own as well as those

imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S. Code Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss, make recommendations and vote on information related to the pre-market approval application supplement for Restylane, sponsored by Medicis Aesthetics, Inc. Restylane is currently approved for mid-to-deep dermal implantation for the correction to moderate and severe facial wrinkles and folds, such as nasolabial folds. The Sponsor is requesting an expanded indication to include use of Restylane for augmentation of the lips.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in connection with 18 U.S. Code Section 208 and Section 712 of the FD&C Act. A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript.

Michael G. Halpin is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Genzyme Corporation.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for

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which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue. Thank you.

Temporary Voting Member Statements.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27, 1990, and as amended August 18, 2006, I appoint the following individuals as voting members of the General and Plastic Surgery Devices Panel for the duration of this meeting on April 27, 2011:

Michael Miller, M.D.

Amy Newburger, M.D.

In addition, I appoint Susan Galandiuk, M.D. as Acting Chairperson for this meeting.

For the record, these individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

This has been signed by Jeffrey Shuren, M.D., J.D., Director, Center for Devices and Radiological Health, on April 5th, 2011.

Ms. E. Paige Brown Strong has been appointed as a Temporary Non-Voting Member of the General and Plastic Surgery Devices Panel for the

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duration of the meeting on April 27th, 2011. For the record, Ms. Brown Strong serves as a patient representative to the Oncologic Drugs Advisory Committee in the Center for Drug Evaluation and Research. This special Government employee has undergone the customary conflict of interest review and have the reviewed the material to be considered at this meeting.

This appointment was authorized by Jill Hartzler Warner, J.D., Acting Associate Commissioner for Special Medical Programs, on April 8th, 2011.

Before I turn the meeting back over to Dr. Galandiuk, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Inc., 1378 Cape St. Claire Road, Annapolis, Maryland 21409, telephone (410) 974-0947. Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

The press contact for today's meeting is Sandy Walsh.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the panel meeting has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Ms. AnnMarie Williams at the registration desk.

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In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time. Thank you.

Dr. Galandiuk.

DR. GALANDIUK: We will now have a brief Panel update from Dr. Danica Marinac-Dabic.

DR. MARINAC-DABIC: Good morning, ladies and gentlemen, Madam Chair, Mr. Melkerson, distinguished members of the Panel. My name is Danica Marinac-Dabic. I'm the Director of the Division of Epidemiology at the Office of Surveillance and Biometrics.

My division is in charge of overseeing all mandated post-approval studies that we ask industry to do at the time of the approval. We also oversee required post-market surveillance studies under Section 522 of the Act, and we conduct original epidemiologic research that is designed to address important methodological concerns for the studies involving medical devices.

I thank you for the opportunity this morning to give you an update on the status of post-approval studies that are conducted under these authorities, and also to report to you what CDRH is doing to advance the methods and infrastructure for studying medical devices in the post-market setting.

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So, as you know, at the time of the approval, FDA has the authority to ask for continuing evaluation and reporting on the safety, effectiveness, and reliability of medical devices for their intended use. We can ask for other requirements, as we determine, needed to address the post-market safety and reliability of devices as they enter real-world practice.

These post-approval studies have enormous public health value, and I think you, as Panel members, have a very important role to play as you make recommendations for what FDA needs to be doing in the post-market setting. So I just would like to remind you that what we are looking for from these post-approval studies are the following:

We would like to gain knowledge about long-term performance of medical devices, including effects of retreatments and product changes.

Also, at the time of the approval, we do not know everything about these devices because the pre-market data certainly have limitations, and as the product enters the real practice, we would like to continue evaluation of the safety and effectiveness in the post-market setting.

Also, the learning curve effects are very important for some devices, and we very often design these post-approval studies to address the effectiveness of training programs and to measure the learning curve effect.

We're looking for subgroup performance because many of the pre-market clinical trials do not have sufficient information about utilization of the devices in certain subgroups.

So these are the reasons, and as you can see, many of these reasons are very unique to the medical device world. Some of these are never an issue if you're a pharmacoepidemiologist working at the Center for Drugs and Evaluation Research, for example.

I'm not going to go into details with the recent developments, but I just would like to, for those of you who are first-time Panel members, just to let you know that CDRH had actually put a lot of effort during the last five or six years to enhance the post-approval studies program, to advance the methods. And, as you can see, we created an integrated post-approval studies program back in 2005 and then, at that time, we started raising the rigor for post-approval studies.

We also developed and instituted a tracking system, and you can find that on our website. We issued a guidance document for post-approval studies. We started with these routine updates to the Panel on how we are doing as a center and how the industry is doing.

We also started inspecting these post-approval studies. Our colleagues from the Office of Compliance are helping us with that. And then recently, during the last two to three years, we have increased our focus on infrastructure building and increased our efforts on methodology development. So, traditionally, these studies have been just a continuation of the pre-market clinical trials and the follow-up.

Right now we are exploring other opportunities. There are

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existing registries in the real world to which FDA had not looked systematically at. We're trying to advise our sponsors that they should look for existing methodologies and existing infrastructure when they think about their post-approval studies.

And as a combination of these efforts, we have launched -- the FDA had launched the MDEpiNet initiative, which stands for Medical Device Epidemiology Network initiative, last year. And I'm going to talk a little about what that entails.

This is the website. I'm sure many of you have looked at that already. It contains the information about these post-approval studies, the progress, the summary of the protocol, and some of the findings for the completed studies.

Just to give you a sense of how many post-approval studies we have asked during the last five to six years, you see here, what is presented in blue are the number of approved original PMAs and panel track supplements from 2005 to present. And what these in red represents is how many instances we asked for post-approval studies. So you can see, we do not always ask for a post-approval study. The decision is certainly made based on the quality of the pre-market data and on the remaining questions that we would like to be addressed in the post-market setting.

But when we decide to ask for a post-approval study, we typically ask for more than one for per PMA, and you know, sometimes we do

have a continuation of the pre-market cohort. The follow-up is sometimes two, three years, sometimes five. For orthopedic devices, for example, 10 years. And that's why what you see here is the number of actual individual studies is larger than the number of the approval orders for including the post-approval study order.

So, to sum up, since 2005 to present, we have issued 186 post-approval study orders and we had 186 studies.

As far as the compliance goes, a vast majority of these studies are progressing well. Eighty-four percent of these studies are progressing on time, and they're good quality studies. In 16% we experienced some delays in enrollment or lost to follow-up, and we work very interactively with the sponsors to help them fix and put those studies back on track.

This is how the situation looks with the general and plastic surgery devices. We have asked, since 2005, for 22 studies to be done under the post-approval study order, and we have a little bit less compliance in this particular setting. And that's certainly understandable, given the nature of these devices and given the fact that many of the patients, when they receive these devices, they are doing fine. They're not going to go back and report that they are fine to their surgeons.

Just to tell you that we have really put a lot of effort in working with clinical societies to identify what are the obstacles so we can help our industry colleagues to deal with them. This is a recently published paper

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authored by colleagues from my group.

As far as focus on infrastructure, I'm not going to go in details, but again, to reiterate, post-approval studies can be done in many different ways, many different designs, but recently FDA is focusing -- CDRH is focusing on utilization of registries. For your reference, here is just a list of efforts with registries and professional societies that we have either a contract or interagency agreement or some type of collaboration where we foster the utilization of the existing registries. And this list continues here. You can see, many of these are from the cardiovascular and orthopedic arena.

We also reach out to our outside of U.S. data sources, and we have relationships with Australian orthopedic registry and Denmark orthopedic registry. And later this month, actually next month, on the 9th we're bringing the heads of more than a dozen international registries to meet with us in creation of an international consortium for orthopedic registries.

In terms of the methods, this is what we are doing. We know that there are challenges on studying medical devices. We have recently published the framework for evidence appraisal for medical devices, which is certainly unique and different than in the pharmacoepidemiology world.

We are also piloting some innovative methods, how one can simultaneously apply a methodology such as meta-analysis, network meta-analysis, cause design synthesis, and helping us put together the best possible

information about the risk/benefit profile in the post-market setting. Once we have these methods developed, we would be very happy to share them with our industry colleagues so they can start applying them in the post-approval studies. This is a recent publication in *Medical Care* that talks about this pilot project.

And finally I would like to add that FDA cannot do this alone. We understand that we have to engage the other stakeholders, and our Medical Device Epidemiology Network initiative has been just geared toward that, to formalize the relationship that FDA has with academia and other stakeholders, so we can together advance the methodology for medical devices. This is our logo. And you will hear more about this, but this is envisioned as a public-private partnership.

So, many of you will be called upon to serve either on the advisory committees or, you know, non-federal partners. As you can see on this slide, there is also industry participation on this. So this is going to be a joint effort on how we can define what are the priorities for medical device research and how we can together advance the field.

These are just some important days. We just had yesterday -- actually on Monday, the second annual MDEpiNet conference, where we talked about this public-private partnership and finalizing the business plan; on May 9th, international consortium of orthopedic registries; and on June 12th the meeting that will tackle diagnostic devices.

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So you as our academia colleagues -- and certainly patient representatives are very crucial, and you'll see a lot of partners coming from patient advocacy groups. And I'd like you to spread the word and help us build this infrastructure and methods that will advance the science, regulatory science for medical devices. Thank you.

DR. GALANDIUK: Thank you, Dr. Marinac-Dabic.

We will now proceed to the Sponsor presentation for Restylane. I would like to remind the public observers at the meeting that while the meeting is open for public observation, public attendees may not participate unless at the specific request of the Panel Chair.

The Sponsor will introduce the speakers. You have 90 minutes.

DR. WORTZMAN: Good morning. I want to thank the FDA and the distinguished Panel for the opportunity for us to present our data for Restylane and the expanded indication for lip augmentation.

I'm Mitchell Wortzman. I'm an employee of Medicis, and I serve as the Executive Vice President and Chief Scientific Officer for the company.

On the screen is our order of presentation, and I would like to take a few minutes to introduce the speakers that you're going to be hearing from.

Dr. Robert Weiss is an Associate Professor of Dermatology at Johns Hopkins and Director of the Maryland Laser Skin and Vein Institute in

Baltimore. He's past president of the American Society for Dermatologic Surgery. He has over 150 peer-reviewed publications and authored dozens of textbook chapters as well as complete textbooks. He also was a principal investigator for the Restylane lip pivotal trials.

Dr. Stacy Smith is a board-certified dermatologist in private practice in Southern California. He's an Assistant Clinical Professor of Dermatology at the University of California, San Diego. Dr. Smith has performed more than 200 clinical trials in aesthetic and medical dermatology. He also served as a principal investigator for the Restylane lip pivotal study.

Dr. Julius Few is a board-certified plastic surgeon. He is the Director of the Few Institute for Aesthetic Plastic Surgery, as well as a clinical associate at the University of Chicago. Dr. Few has more than 50 publications and serves as a Clinical Editor for the *Aesthetics Surgery Journal*, Commissioner of Cosmetic Medicine Board of Directors in the American Society for Aesthetic Plastic Surgery, as well as a medical advisor for ABC News.

Dr. Ira Lawrence is our Chief Medical Officer at Medicis and Senior Vice President of Research and Development, with responsibility for regulatory and medical affairs. Dr. Lawrence is a board-certified internist and clinical immunologist.

And Ms. Xiaoming Lin is our Vice President of Clinical Research and Development at Medicis. She holds advanced degrees in clinical science

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and nursing, and Ms. Lin has over 15 years of experience in the design and implementation of clinical trials.

To provide you a little bit of background to today's presentation, Restylane is a trade name for a hyaluronic acid-derived dermal filler originally produced by Q-Med in Uppsala, Sweden. Medicis acquired rights to the development and distribution to Restylane in 2003, and we are in Arizona, a Scottsdale, Arizona-based corporation.

Restylane was first approved for marketing and sale in the EU and various other countries in 1996 and, since its initial approval, has been marketed worldwide in over 70 countries around the world. Restylane was approved in the U.S. in December 2003 and is currently indicated for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as the nasolabial fold. A duplicate PMA was issued in March 2005 for the same indication for regulatory reasons with our Swedish partner, Q-Med.

Today we're here to present data to support the expanded indication, adding to our current indication to read: for submucosal implantation for lip augmentation.

I'd like to turn the podium over to Dr. Weiss, who will take us through some of the medical background of Restylane.

DR. WEISS: Thanks very much. Good morning. By way of disclosure, I'm here today as a consultant to Medicis. My primary occupation

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is seeing patients in my office in Baltimore. And I'd like to provide a little bit of clinical background to the data that is going to be presented here today.

We've had a lot of experience with hyaluronic acid. It's frequently sought and commonly used in clinical practice. It's used widely around the world for lip augmentation at this point in time.

According to a recent survey in 2010, there were over 1.2 HA procedures performed in the U.S., 1.2 million, and we published in *Facial Plastic Surgery* in 2009. At that time we had the statistics of tens of millions of dermal filler treatments performed worldwide, most importantly, 85% of which are with hyaluronic acid.

The demographics of patients seeking soft tissue filler procedures are predominantly female, 95%, and they are predominantly over the age of 40, although there are small subgroups, the smallest being 13 to 19 years old comprising 1%. And this is according to the statistics of the American Society of Plastic Surgeons.

The ethnicity breakdown for cosmetic procedures is 70% or approximately two-thirds Caucasian, with the remaining being split between Hispanic, African-American, Asian-American, and other. Again, this is according to the American Society of Plastic Surgeons report in the 2010 plastic surgery statistics.

In terms of looking through the literature, in terms of finding literature with references to lip augmentation, if you type lip augmentation

into the pubmed.org site, you'll come up with 344 publications. And actually I was doing this yesterday. If I put in hyaluronic acid, you'll come up with actually -- and filler or hyaluronic augmentation, you definitely expand the number of publications that come up.

We know that in 1986 there was the first publication of lip augmentation using a temporary filling substance at that time, bovine collagen. And there's also been extensive European use of hyaluronic acid for lip augmentation, which was initially published actually in several different journals if you go back to 1998, and we've listed those references in the slide presentation.

Publication of U.S. practice review -- and again, that publication is referenced on the slide and it should be in your notes -- shows that 51% of HA dermal filler users received lip augmentation. So typically in my practice -- and I do several thousand hyaluronic acid treatments a year -- I would say it's roughly a similar percentage. So maybe 35 to 40% of the patients that I'm injecting for nasolabial folds, I'm also doing lip augmentation. So I've had some pretty extensive experience over the last five or six years.

A recent ASAPS survey showed a significant percentage of use of HA fillers in the U.S. is for lip augmentation. So that concurs with the report that was published in 2008.

And, additionally, there was a multi-specialty facial plastic,

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plastic dermatology, the ophthalmoplastic meeting in Washington, D.C., where we got together to kind of point out some of the deficiencies in our understanding of the use of fillers and reporting of safety.

And so there was a rather lengthy publication, which fortunately got cut down in the editing process, which was simultaneously published in the *Journal of the American Academy of Dermatology*, and *Plastic and Reconstructive Surgery*, and that was recently published in 2011, like a month or two ago. But one of the primary conclusions in the section about what can we do to enhance our knowledge was to encourage industry to fund prospective studies on new and expanded indications, standardize validated methods for assessing outcomes, and involve appropriate representative patient types, all patient types as listed on the ethnic analysis slide that I showed before.

So, in summary, as we sit here today, this morning, there are probably hundreds of lip augmentation procedures that are going to occur or are occurring around the world today. But what we need is we need data on the effectiveness and safety from well-controlled prospective studies to provide guidance for both physicians and for patients.

And certainly, as a non-Medicis employee, I really applaud Medicis for really putting in all of the effort, because we participated in the study and you'll hear about all of the details that, you know, this pivotal lip study really serves the purpose and sort of anticipated the needs of the Panel

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and the proceedings that were just published.

So with that, I would like to hand the podium over to Ms. Xiaoming Lin, who is going to go over the development of this program and its background.

MS. LIN: Thank you, Dr. Weiss.

My name is Xiaoming Lin, and I'm a full-time employee at Medicis. Today I'm going to talk about program development and provide some background information.

Here is the program chronology. At the very beginning of the program, we did the first U.S. lip pilot study. That study is MA-1300-13K. We did that back in 1996.

And then Medicis developed and validated the Medicis Lip Fullness Scale. And from now on we're going to refer to it as MLFS. And after that scale developed and validated, we used the scale in another pilot study, which is a Canadian pilot study. The study number is MA-1300-14.

And, finally, Medicis designed and conducted the U.S. pivotal lip study. The study number is MA-1300-15.

The first pilot study for this whole program is MA-1300-13K U.S. pilot study. The main purpose for this pilot study is to assess the safety profile using Restylane for lip augmentation in a controlled clinical setting. And MA-1300-13K is a 20-subject, prospective, open-label, single-center, evaluator-blinded study to assess the efficacy and safety using Restylane for

lip augmentation.

Here are the highlights for the study efficacy result. Using the GAIS assessment -- GAIS is Global Aesthetic Improvement Scale -- and from now on we're going to refer to it as the G-A-I-S or GAIS.

Per subjects' assessment, 100% of the subjects rated themselves as having improvement through week 12, and 74% of the subjects rated themselves as having improvement through week 24.

How about treating physician's assessment? Using the same GAIS, 100% of the subjects have improvement, according to GAIS, per treating physician's assessment, and 84% of them have improvement, according to physician's assessment, through week 24.

Safety-wise, mass formation was reported in 90% of the subjects' diaries. This is reported to the Sponsor by the PI that this is the result of a miscommunication with the subjects. PI reported it to us that subjects were told to report any product palpability as a mass formation. And the PI pointed out to us, none of these mass formations was reported as AE by the subject or observed by the study personnel.

But Medicis still takes this information very seriously, and in our pivotal study design we specifically include mass formation assessment for all post-treatment visits, and this assessment is done by a medical professional. In our pivotal studies we had one subject who had one mass formation event resolved within one visit.

And overall we had six treatment emergent adverse events. From now on we are going to refer this as the TEAE. These six events were experienced by three subjects. Two of these events are considered related to treatment. Both of these events were mild bruising. The over-conclusion of the first pilot study, a single treatment using Restylane for lip augmentation was well tolerated.

After the first study, Medicis went ahead and developed and validated the MLFS scale. From the very beginning of the scale development, Medicis focused on creating a scale that is clinically relevant and clinically meaningful for physicians, and Medicis achieved this goal by working closely with board-certified dermatologists and plastic surgeons.

And there are two main goals of the MLFS. First, the physicians could use the scale to communicate the treatment goals with the patient in the study. Second, the evaluators could use the MLFS to assess the effectiveness results for lip augmentation.

Medicis also worked very closely with the FDA during this process. Results were presented and discussed with FDA at the pre-IDE meeting on September 4th, 2008, and included in the approved IDE. The scales were accepted by FDA as a validated tool for effectiveness measurement for lip augmentation.

Here are the five grades for the MLFS, from very thin, thin, medium, full, to very full.

Here are some examples of the photo guide. This is a sample of a very thin upper lip. In order to avoid confusion, the lower lip is pixelated out for the upper lip photo guide photos.

Here is a sample of the thin upper lip. Here is a sample of the medium upper lip, full upper lip, and very full upper lip.

Here are some examples for the lower lip photo guide. This is an example of a very thin lower lip. Again, in order to avoid confusion, the upper lip is pixelated out in the lower lip photo guide.

Here is an example of a thin lower lip, medium lower lip, full lower lip, and very full lower lip.

After the scale's developed, Medicis went ahead and did the scale validation. Medicis actually did two rounds of the validations for the MLFS. The first round of validation is a photographic assessment of validation. The purpose of this round of validation is to assess if the MLFS could be used for photo assessment. The second round assessment -- the second round validation is a live assessment versus a photograph assessment validation. The purpose of this round of validation is to assess if MLFS could be used for live assessment as well as photo assessment.

Validation results are displaced using weighted kappa coefficients. Here is how we interpreted a weighted kappa coefficient. According to Landis and Koch, and also discussed with the Agency, the weighted kappa value over .6 represents a least substantial agreement.

This is how we did the first round validation for MLFS. The first round is a photographic validation. We involved five evaluators, using 85 photos for upper lip and 85 photos for lower lip. Each evaluator did two evaluations, and those two evaluations are at least two weeks apart.

Photos used for validation represent a lip's range from very thin to very full, different race, different age, and different gender, and different Fitzpatrick skin types. Each photo had a unique identification number and the sequence of the photos were randomly assigned for each round of evaluation.

Here are the results for the first round MLFS validation. For within rater reliability, also called intra-rater reliability, agreement was substantial to almost perfect. For the upper lip, the weighted kappa values varied between .7 to .87, with overall value .81. For lower lip, the weighted kappa values varied between .63 to .9, with overall value .81.

What does this mean? These results confirmed that MLFS can be used consistently by the same evaluator at different time points.

Here are the results for between rater reliability or inter-rater reliability. The agreement was substantial. For upper lip, the weighted kappa values varied between .6 to .83, with overall value .72. For lower lip, the weighted kappa values varied between .59 and .81, with over-value .69.

What does that mean? This means these results confirmed that MLFS can be used consistently by different evaluators.

Medicis went a step further. Per request of FDA, Medicis did the second round of the MLFS validation. This round is a live assessment versus a photographic assessment validation. The purpose of this round of validation is to assess if MLFS can be used for live assessment as well as for photo assessment.

For this round of validation we involved three evaluators, involved 39 subjects for upper lips and 39 subjects for lower lips. And the subjects represented again a full range of lips, from very thin to very full, different race, age, and genders, and different Fitzpatrick skin types.

The first evaluation of this round of validation is a live assessment. Three evaluators assessed the subject's lip fullness in person. A second assessment is a photo assessment. The photos were taken for the same subjects at the end of the first round of evaluation. The photos were sent to the evaluators two weeks later, and the sequence of photos were randomized and assigned.

Here are the results for the second validation. For the within rater reliability, the agreement was substantial. For upper lip, weighted kappa values varied between .62 to .68, with overall value .65. For lower lip, weighted kappa values varied between .61 and .68, with overall value .64.

What does this mean? These results confirmed that MLFS can be used for live assessment as well as for photo assessment. This is very exciting news for us.

For overall summary, the validation results showed that MLFS can be used by different evaluators consistently, by same evaluators at different time points consistently. The results also showed that MLFS can be used for live evaluation as well as for photo evaluation.

Due to the results, Medicis designed the U.S. pivotal study including live assessment using MLFS, such as a blinded live evaluator's assessment, treating physician's assessment. We also include photo evaluations in our pivotal U.S. lip study, such as independent photographic reviewer's assessment.

The overall conclusion of all of this work is that a five-point MLFS is suitable for use in clinical settings for effectiveness measurement.

After the validation's done, Medicis did a second lip pilot study in Canada. The main purpose of this pilot study is to use MLFS in a clinical study and to assess if a one-grade improvement of MLFS is clinically meaningful. This is a very important question for us and for the physicians.

MA-1300-14 is a second pilot study. This is a 21-subject, open-label study in Canada to assess the effectiveness and the safety using Restylane for lip augmentation.

Here are the highlights of the efficacy results. Using MLFS assessment at week 8, 89% of the subject at least a one-grade improvement in both upper and lower lips per blinded evaluator's assessment as well as per treating investigator's assessment. The study shows the effectiveness results

maintained throughout the 12 weeks of the study.

We also did a GAIS assessment for this study as well. At week 8, 100% of subjects had improvement per GAIS, by blinded evaluator's assessment as well as by treating evaluator's assessment. Subjects most often are quite hard on those kind of assessments.

For this study, 94% of the subjects rated themselves as having at least a one-grade improvement by GAIS at week 8. At all other study visit points, for example, week 2, 4, and 12, at least 80% of the subjects had a one-grade improvement per GAIS, evaluated by subjects themselves or by treating physician or by blinded evaluator.

GAIS is very widely used in clinical trials, especially clinical trials like this. GAIS is also widely accepted. That one-grade improvement per GAIS represents a visible clinically meaningful aesthetics improvement.

So Medicis did an assessment between the agreement of MLFS and GAIS in this study. At week 8, we have 100% agreement between MLFS and GAIS. For upper lip and for lower lip, we have 89% of the agreement. The higher agreement proved that a one-point move of MLFS is clinically meaningful and the difference is visible as well.

The safety summary for the second pilot study, we had eight AEs reported by six subjects, and we did not have any SAEs reported, and it showed that the treatment using Restylane for lip augmentation was well tolerated.

So what's the overall summary of all the early development work here? The overall summary is Restylane for lip augmentation is highly effective and has an acceptable safety profile. The early work also confirmed the clinical utility of the MLFS and it also showed a one-grade improvement in MLFS represents a clinically meaningful result.

After all of this, we designed the U.S. lip pivotal study MA-1300-15. That's the main reason why we are here today. This study is really a very robust study design. Medicis incorporated all the FDA's questions, suggestions, and requirements into this study design. This is a randomized, evaluator-blinded, no treatment as a control study to assess the effectiveness and safety of Restylane for lip augmentation.

There may be a question why you choose no treatment as a control. Medicis actually had a very lengthy discussion with FDA during the pre-IDE and IDE process. We decided that no treatment as a control is most appropriate for this study because there's no product, no dermal filler approved in the U.S. with a lip indication. And also we could not get agreement on what is the standard of care for lip augmentation.

And if we remember, in 2009, open FDA panel there, there was a discussion that a fat implantation may not be appropriate for lip augmentation as a control arm here. That is why we chose the no treatment as a control for this study. And also we did not think it's really ethical to poke the patients with the needles in the lips without any benefits for the patients

there.

The MA-1300-15 is designed to enroll 180 subjects at 12 U.S. centers. It is designed to enroll at least 30 subjects with a Fitzpatrick Skin Types IV, V, and VI. Subjects are randomized to a three-to-one ratio into this study, three for Restylane treatment and one for no treatment.

Here is the Fitzpatrick Skin Type Scale. Fitzpatrick skin type mainly is decided by the color of the skin, whether the skin burns or tans after sun exposure.

Subjects for this study, subjects randomized to Restylane treatment at baseline received a second treatment at six months. This is to assess whether it's a different profile for safety for retreatment. Subjects randomized to no treatment at baseline received their first treatment at six months. And the safety of all subjects was monitored throughout the study.

Here are some general inclusion criteria for this study. The subjects needed to be 18- to 65-year-old males or females; no confounding facial plastic surgery or cosmetic procedures for the duration of the study.

For the Fitzpatrick Skin Type I, II, or III, subjects need to have both upper and lower lips to be very thin or thin to be qualified for the study. For Fitzpatrick Skin Type IV, V, or VI, subjects need to have at least one of the upper or lower lips to be thin or very thin to be included in the study. It was decided in such a way because it is very, very difficult, if not near impossible, to enroll a decent number of subjects with a Fitzpatrick Skin Type IV, V, or VI

with both lips thin or very thin.

The recommended dose for this study is 1.5 mL per lip per treatment session. And FDA recommended to us to put in the optimal correction in the protocol, and we did, and we think it's a wonderful suggestion.

In the protocol, we ask the treating physicians to treat the subjects to the optimal result, and to the optimal correction is defined as the best possible aesthetics results agreed by both patient and treating physician. This is a very high hurdle here.

Here is the primary endpoint. The primary endpoint is to identify whether Restylane was more effective than no treatment to group in lip augmentation at week 8. This is determined by the live blinded evaluator using MLFS for assessment. This result is compared to the baseline MLFS result performed by the treating investigator. This is done per FDA's request to enhance the blinding.

This way, the blinded live evaluator did not know the treatment sign of the subject, did not have any knowledge of the lip fullness of the subjects at baseline. The blinded evaluator did not do any other study activities but the assessment of MLFS from week 8 on. By week 8, the commencing AEs in the lip area, swelling, redness, are all gone, so the blinded evaluator could not be potentially unblinded. And the treatment success was defined as at least a one-grade improvement on the MLFS in both upper and

lower lips, a higher hurdle to achieve to reach the treatment success here.

We have several secondary effectiveness endpoints using the MLFS in the study as well: for example, blinded evaluator assessment at week 12 through study end -- week 8 is the primary endpoint -- and the treating physician's assessment at all study endpoints except a 72-hour safety visit. Seventy-two hours is specifically designed for safety visit there. And also independent photographic reviewer's assessment at the very end of the study, using the photos taken at baseline, at week 4, 8, 12, 16, 20, and 24.

When I said this is a robust study design, for example, the blinded evaluator -- the blinded photo evaluator, each of them assessed over 2,000 pictures for this study.

FDA asked us to clarify the photo-naming conventions for Panel members here. To enhance the blinding of the study, subjects' photos were named generically. For example, at week 24, the visit was called 24-week follow-up treatment, and 72 hours post-treatment. If the subjects showed up for that visit, even if they were not treated, the photos are still named this way there. It is done to enhance the blinding for the study.

We also used the GAIS for some secondary assessment here. GAIS were done by treating physicians and the subjects, not the blinded live evaluators. And at all the post-baseline time points, and they use the baseline photos for reference. Because they use baseline photos for reference, we did not ask the live blinded evaluators to do the GAIS

assessment. Responders of GAIS is defined as a one-grade improvement or better in the upper or lower lips or combined.

We have a robust study design for the safety assessment there. We have three endpoints for safety assessment. One is AE collection throughout the study. Second is a 14-day subject diary at baseline and at month six. And also Medicis has specifically designed nine specific lip safety evaluations. I want to say how robust the study design is. Just for the last lip safety evaluations, we have over 60,000 data points just for the lip safety assessment.

Now I would like to turn the presentation over to Dr. Ira Lawrence.

DR. LAWRENCE: Thank you, Ms. Lin. And good morning. It's a pleasure to be here and join you. I have the distinct pleasure of discussing the efficacy or effectiveness data on the pivotal trial that we are utilizing to seek our indication expansion.

By way of introduction to the trial, this study enrolled a total of 180 subjects, 135 of whom were randomized to receive Restylane at baseline, 45 of whom received a no treatment arm at baseline. The mean age was 47.6, very similar to the demographics Dr. Weiss has discussed. The vast majority of patients were female and Caucasian. One hundred and thirty-nine of these subjects were Fitzpatrick Skin Types I, II, and III. And actually we exceeded the original goal of at least 30 by having 41 subjects who were

darker skin tones, Fitzpatrick Types IV and V.

The Restylane treatment group, by way of introduction for volumes, as you know, the recommendation was about one and a half per lip per treatment. You can see here that the initial treatment for the upper and lower lips combined was 2.3, touch-up treatment less, at .8, and then the overall initial treatment and touch-up for total volume was a mean for both lips of about 2.9 mL.

Again, similarly at the retreatment point, which occurs at six months, you can see again the combined upper and lower volume used at the initial retreatment visit is 1.5 mL, a touch-up two weeks later at .7, and a total at both points for the retreatment of 1.8 mL.

There were two instruments that were utilized for our effectiveness tools. The first was Medicis Lip Fullness Scale, which Ms. Lin has discussed extensively. This was utilized both by the live blinded evaluator and also the independent photo reviewer assessment as well as the treating physician.

It's important to note that, for the blinded evaluator, this is a static assessment. So the patient is actually evaluated for their rating on the MLFS at that point in time. It is not compared to the baseline, so it is a static -- a very rigorous standard.

We also utilized a Global Aesthetic Improvement Scale, the GAIS. This is a live assessment conducted both by the subject and the

treating investigator. They are permitted to review the baseline photographs in order to determine their improvement. We believe this is important. In large part, as a panel in 2009, the challenge was actually to ensure that not only are we meeting a quantitative improvement but also that patients are achieving a desired improvement.

Very briefly, this is the GAIS Ms. Lin alluded to. It is actually a seven-point scale. We rate any patient who rates themselves as having an improvement or above as having been a responder on the GAIS.

The primary endpoint for this study was at week 8, utilizing the blinded evaluator MLFS assessment. You can see here, utilizing both the upper, lower lip, and the lips combined, a very high number of patients were rated as a responder, that is, they had at least a one-point improvement on the MLFS.

Again, here you can see in the no treatment arm a range of about 30 to 35%. This is actually not uncommon in aesthetic studies, where there is a little bit softer endpoints, but again, very consistent with our previous experience in such studies.

Here you can see a graphical representation of the data. The first column here is the week 8 primary efficacy endpoint. You can see here a very dramatic difference between the treatment arm and the non-treatment arms, very highly statically significant at less than 0.001. And, in fact, this significant difference was maintained throughout the course of

the study so that all data points throughout the 24 weeks of the study, pre-retreatment, reached a statistical significance of less than 0.001.

Therefore, the difference in proportion of the MLFS responders from baseline, utilizing Restylane versus no treatment, is highly statistically significant, and thus the primary effectiveness endpoint was met, which would demonstrate that Restylane is highly effective for lip augmentation as predefined.

It is also important that we collected a number of secondary endpoints. In these cases, the differences between the Restylane treatment arm and the no treatment group is highly statistically significant, in favor of Restylane treatment at all time points throughout the 24-week period of the study. This includes the data from blinded evaluators, treating investigators, and the independent photo assessments. Again, all of them are highly statistically significant.

Here you can see the proportion of responders when you compare them utilizing the independent photographic reviewer. You can see, at week 2 -- or, excuse me, week 4, about 75% of the patients are rated as responders by the photographic reviewer. And the statistically significant advantage versus the no treatment arm is maintained throughout the study.

I do want to note that it is not infrequent for independent photo reviewers to have a more compressed or lower rating. They are having the disadvantage of only have a two-dimensional evaluation, as opposed to

the live evaluator, who has the advantage of a three-dimensional or a live patient evaluation.

Similarly, you can see here in the treating investigator, who of course was not blinded, again, a very similar highly statistically significant advantage for responders versus the no treatment arm, and the statistical advantage was maintained throughout the course of the study.

We also utilized a measurement of aesthetic improvement, which allows us to understand how the patient feels they have achieved their stated goal of optimal improvement. We think that this is a very, very important part of a study, especially an aesthetic study where patients need to make sure that they are achieving their desired goals. This was assessed by both the subjects and the treating investigator using baseline photos for reference.

And again you can see here, as rated by the subjects, beginning at week 4, a very high amount of improvement as rated by the subjects. This was maintained actually at almost 75%, even out to week 24, and again highly statistically significant, again showing that the patients had a high degree of satisfaction and recognized the improvement to their satisfaction at all points.

A similar amount of improvement is noted by the treating investigator throughout the course of the study, and again is highly statistically significant.

It is also, I think, very powerful that in this study all of the evaluators came to the same conclusion, whether it be the blinded evaluator, the treating investigator, or the independent photo reviewer. All of them independently came to the conclusion, based on the statistics that we had provided, that Restylane for lip augmentation is highly effective. Subjects and treating investigators further confirmed that this was aesthetically meaningful by the high GAIS scores that we achieved.

As I mentioned earlier, there is a note about the differences in the ratings between the evaluators. This is not new or unusual in the dermal filler programs. In fact, at a 2003 FDA open public panel, this was discussed and agreed that this is one of the issues. This has also been described frequently in published data, and we actually include one such reference on your slides.

I think the most important thing is that we feel strongly that the blinded live evaluator assessment is in fact the most important and reliable. It is reliable and accurate. It uses a validated scale, the MLFS. This individual is most able to examine the subject's lips fully, although it's important to note that in this study they did not touch the patient, but they were able to evaluate them, have them move and position their lips optimally for the study.

They are also very importantly blinded to baseline lip fullness, so they have no parameter. They just have a static evaluation at the point in

time that they're looking and evaluating the patient. They are blinded to treatment assessment, and they're also blinded to the total volume utilized. This is also, of course, our predefined primary endpoint.

All of the effectiveness endpoints are consistent and highly statistically significant, as I've mentioned, by all evaluators, regardless of the tools utilized, either the MLFS or the GAIS, and throughout the 24-week period of the study.

Just a few representative patients, and I think you have these in your folder, as well as many more. This is a 52-year-old woman. You can see here, at baseline and then by week 8, at least a one-grade improvement in her fullness of her lips. And here you can see, again, at week 24. It's important to note that this patient actually chose not to receive retreatment at week 24. She was completely satisfied with the aesthetic result she had received at that point in time.

This is another patient. Again, you can see here a comparison of the thin lips at baseline versus, at minimum and certainly more, I believe, a rating of improvement of one grade at week 8. And, again, here you can see her at week 24, when she did choose to receive retreatment to continue to maintain her lip fullness.

So, in summary, Restylane, as demonstrated by our pivotal trial, is highly effective for lip augmentation and provides a clinically meaningful and visible aesthetic result for a period of at least six months.

These results are demonstrated by the blinded evaluator and confirmed by the treating investigator and the independent photo reviewer using the MLFS. These results are also further confirmed, especially from the standpoint of aesthetic improvement, by the rating of the investigator and the subject GAIS.

It is now my great pleasure to introduce Dr. Stacy Smith, who will be discussing the safety assessments we conducted in the study.

DR. SMITH: Thank you, Dr. Lawrence. Good morning.

For the purposes of financial disclosure, I have served as a consultant to Medicis Pharmaceuticals. I was a principal investigator on the lip augmentation study. I am being compensated for my time and travel for today's meeting. I have no equity interest in the company, however.

The safety data that was compiled during the study is basically split into three components. First is the adverse event reporting system that is traditional for all clinical research studies, whereby patients ask open-ended questions and examine. Those events are recorded by the evaluating physicians. There's also a subject diary. And lastly there was the specific battery of lip safety assessments that was designed specifically for the study. And I'll discuss each of these in turn.

Looking first at treatment emergent adverse events, or hereafter TEAEs, we're going to split these into three components or three groups, and we're going to be seeing these again and again.

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The first group comprised those subjects who had their first Restylane treatment. That would be the individuals randomized to receive Restylane at the beginning, as well as those subjects who were randomized to control but did receive their first Restylane at the 6-month or 24-week time point.

The second group are those patients who had a second Restylane treatment. So those are the individuals randomized to receive Restylane at the beginning and then at six months had their second Restylane treatment.

And the last group, of course, is the untreated controls, those individuals randomized to the control portion of the study for the first six months.

Here we can see the proportion of treatment emergent adverse events. These are both related and unrelated to treatment, so basically all adverse events. And in the first Restylane treatment group we see a proportion of 87% of individuals having experienced at least one TEAE. Moving to the second Restylane treatment group, we can see that the proportion is less, 65%. And then, not surprisingly, the untreated control group has the reduced proportion of treatment emergent adverse events at 38%.

Looking more specifically at the common adverse events, and those are mostly in the lip area, we see six common findings here, namely,

pain, swelling, tenderness, the word contusion, which is a grouping of both ecchymosis and bruising, erythema, and skin exfoliation. It's important to understand that skin exfoliation represents simple desquamation or peeling of the vermilion portion of the lip. This is not epidermal necrosis or other more severe findings.

What we did see is the proportion of subjects with these common lip area TEAEs appear to decrease from the first treatment group to the second group.

Here they are represented graphically. The blue bars represent the first treatment group, the red bars represent the second treatment group. Swelling was most common, at 50 and 60%, followed by that contusion or bruising and ecchymosis portion, and then the other findings are less frequent.

Overall, I think you can see that the red bars are at least no greater than the blue bars, indicating that the second treatment appeared to be better tolerated than the first.

Looking now at the severity of treatment emergent adverse events, now we're looking not at the proportions of subjects but total number of events, there were 1,088 events during the study. The overwhelming majority were mild at 88%, 11% were moderate in character, and just 1% were severe.

Here are four groupings. The bars to the left are the data I just

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told you about, 88 and 11%, with the 1% severe. The next two groupings represent the control group as well as the first Restylane treatment group. And hopefully you can see that the proportions are all very similar between these three groups. The last group to the right is the second Restylane treatment group, and hopefully you can see that the proportion of mild adverse events is greater and that moderate and severe adverse events appear to be less frequent.

Looking now specifically at those severe adverse events, there were a total of 10 events in the study in eight subjects. First, those that are treatment related, that was three subjects and a total of five events. Four of those events were pain; one event was swelling. Because they were felt to be related to treatment, they occurred very early, the first one to two days of treatment, their duration was short, a maximum of five days, and most importantly, they were managed with over-the-counter pain medications only. There were no narcotics required and no other concomitant procedures to allow these adverse events to resolve.

The unrelated severe adverse events, not treatment related, a total of five subjects with sort of random, different causes here. Importantly, they occurred more than 30 days after treatment in most cases because they were felt to be unrelated, and they had a maximum duration of eight days.

Subsequent to the study, we were asked to take a look at or understand the correlation or potential correlation between the volume of

material used and the adverse event profile. What we did was look at the volume used in the initial treatment injection, not in the touch-up injections and not in the retreatment, and what was noted is there was a trend towards a greater proportion of more moderate adverse events depending on the dose or volume of material that was put into the patient. Looking at severe adverse events was fruitless in that there were not enough of those events to make any conclusions.

Graphically, here is that information separated into groups. Here we have, at the far left, less than one milliliter of material, then one to two milliliters of material, two to three milliliters of material, and so on. The blue bars represent mild adverse events. The red bars again represent moderate adverse events. And I think it can be seen that the proportion of moderate adverse events increases with volume, reaching between 45 and 50% in the three to four and four to five mL group, respectively.

We looked at the distribution of adverse events. We looked at their severity. Now, what about their duration? Looking again at common adverse events, those greater than 5%, they had a mean duration of less than 15 days, and there was a trend towards the same or better duration in these adverse events in that second treatment group.

Here is five of the more important, if you will, adverse events, swelling, pain, contusion again, which is bruising and ecchymosis together, tenderness, and skin exfoliation. And, in general, you can see the mean

values for the durations between the first treatment and the second treatment are the same or at least no worse in the second treatment group, except for perhaps skin exfoliation. The skin exfoliation group in the second treatment group represents two patients and potentially explains some skewing of the data.

Looking now at the serious adverse events that occurred during the study, a total of five serious adverse events only in the study. Their causes are listed here. Most importantly, none of them are felt to be related to the procedure or to the device. There were no deaths reported during the study, and there were no subject discontinuations in the study for any level of severity of adverse events.

The second component of this safety data compilation, if you will, are the subject diaries. Subjects were given diaries at the baseline and at six months. They were asked to complete these diaries for 14 days. The diaries were composed of six different elements or symptoms that are commonly seen with dermal filler treatment: bruising, redness, swelling, pain, tenderness, and itching.

The subjects were asked to assign a level of severity to each of these symptoms or findings, if that they had that. None, tolerable, affecting daily activities, or disabling were those choices for severity. It's very important to understand that the subjects were not pre-educated. These levels of severity were not predefined. This was done on purpose to allow

the subject to openly express their interpretation of what this meant to them.

Looking at the percentage of subjects who had some level of severity reporting in their diaries, on the left we see the first treatment group, on the right we see the second treatment group. This is any maximum value of entry in their diary.

Looking first at the first treatment group, we see that about half the patients had the maximum level of severity of any event in their diary of tolerable, and that's about 50%. Looking at affecting daily activities or disabling, there were smaller percentages, 36 and 10%, respectively.

More importantly, turning our attention to the second treatment group, we see that, overall, the level of severity appears to have improved, where now 67% of the patients have a maximum diary entry of tolerable and then smaller proportions for those affecting daily activities or considered disabling by the patient.

Looking now at the total of all the diary entries, remember that patients could record none if they had no bruising, swelling, et cetera. If we look at a compilation of all of those diary entries, again, the first treatment group to the second treatment group, we can see that 71% put none for any one of these particular findings.

Looking at the tolerable events, we saw about one-quarter were listed as tolerable and then a very small percentage, 2.78%, were in the affected daily activities category and .24 in disabling. Just like we saw with

the percentage of subjects with a particular maximum finding, we see an improvement in this proportion. More of the events are tolerable and more of the events are none in the second treatment group as compared to the first treatment group.

It's very important, since we have these affecting daily activities and disabling events, how long these last. Here's the duration of these symptoms or findings in the diary. The vertical axis here is 14 days, to represent the entire duration of the diary. And we can see that the mean duration is 2.2 for the first treatment group, for those that were considered affecting daily activities, and it becomes smaller for disabling and again smaller for the second treatment group. Overall, none of them greater than two and a half days on average.

So, in summary, looking most specifically at these more severe categories of ratings by the patients, those affecting daily activities and/or disabling, it's important to understand those parameters were not predefined, so the subject could interpret those in any way they saw fit. Most of those started directly after treatment. I just showed you, they're very short in duration, less than two and a half days on average for any one of them. And most importantly, subjects who had this categorical rating of some finding, the overall majority, almost all, 97%, when you looked at their GAIS rating for themselves at two weeks, almost at the same point in time they're filling out these diaries, rated themselves as improved or better, were

considered a responder with respect to the Global Aesthetic Improvement Scale.

Lastly, another way to assess whether or not they were satisfied is, did these subjects undergo retreatment? In the study, overall, 80% of subjects underwent retreatment, and the proportion of subjects who underwent retreatment who had an affected daily activity or disabling event in their diary was similar, at 78%.

To help the Panel characterize what this looked like, here are some examples. This is a 45-year-old woman who had two cc's of Restylane injected at baseline. In between the picture on the left and the picture on the right, which is at 72 hours, she did have a diary entry of disabling lower lip swelling for one day.

Here she is 72 hours and two weeks later. She also had an adverse event of moderate upper and lower lip swelling that resolved after day nine, in between these two photographs. Also in between these two photographs, she did assent to her touch-up treatment, which is an additional two cc's of the material.

Another example. A 52-year-old female had to 2.8 cc's of material injected at baseline. She had diary entries for the entire period of the diary, from day 1 to day 14, of affected daily activity severity for lip swelling and lip tenderness. You can see, at 72 hours, those events were ongoing for her. She had no adverse events recorded by the evaluators. And

then, in between the 72 hours and the two weeks post-treatment, she also underwent touch-up injections with 0.4 cc's of Restylane. So despite having diary entries, affecting daily activities, she did assent to touch-up treatments.

All right, the final component of our safety database is these nine lip safety assessments. These are specific tests or tools developed just for this study, to help understand lip safety and lip function. As was stated before, these were done by each patient at every visit, so they represent approximately 20 or more evaluations for each individual component and a total number of data points of over 67,000 throughout the study. These were done by the study site staff.

First is lip texture. This was done by observation of the patient. They can be normal or some degree of abnormal, based on their appearance. Here's the data throughout the study. Not surprisingly, they began after injection and were seen at the 72-hour time point, very small in percentage, and resolved promptly over about the four-week time frame. Most were mild in character.

Looking at lip firmness, similarly, they can either be normal or abnormal, based on a range. This was done by palpation of the patient, again, by study site staff. Here are the findings. Again, related to injection; seen at 72 hours; not seen at screening; slowly waning over time; most of these lasted four weeks or less and were mild in character.

Lip symmetry was done by actually measuring the patient, and

this is lip symmetry, not from upper lip to lower lip, but from right side of the lip to the left side of the lip, and this was done for a vertical component as well as the lateral or width component of the lip.

It's important to note that you could enroll in the study with mild lip asymmetry, so we do see some abnormalities in red at the screening visit. Their proportion increases after injection. And then by about week 4 or week 8, the proportion of lip asymmetric individuals is fairly similar to the screening period. It's felt that a lot of this was due to lip swelling.

Lip movement was assessed by asking the patient to pronounce specific words. These words were chosen after consultation with the speech therapy literature to choose those words that tested lip apposition to each lip, one another, as well as to the teeth. There were exactly three episodes where a subject could not pronounce one or more of the words, one at week 16, one at week 24, and one at the end of the study.

Lip function was assessed by asking the subject to drink through a straw, and they were observed and made sure that they could take the water up through the straw and that it wasn't dribbling or leaking. There were no abnormalities in the lip function test.

Lip sensation was tested in two manners. One is with a monofilament strand. This is done typically in the world of neurology. A fine monofilament strand is touched to the skin and deflected. That deflection yields, in this case, a 0.4 gram level of pressure. Additionally, a small wisp of

cotton was used to test their ability to sense light touch. The subjects were blindfolded during these tests. They were tested at three different points on the upper lip and lower lip, respectively.

For the monofilament tests, there were only two abnormal events, one each at week 12 and week 16. And for the cotton wisp test, there were no abnormal findings throughout the study.

Device palpability is important. In the world of dermal fillers, it is normal to be able to feel the product underneath the skin or in the lip, and it's important to understand that. There is normal feel, but there is also abnormal feel. Abnormal feel would be lumpiness or non-uniformity in the density or feeling of the material within the area which is injected. Also, if the material is gone, in fact, you would not be able to palpate it. So the answers here for palpability were either no, you didn't feel it, yes, you felt that it was normal, or yes, you felt it and it was abnormal.

Here's the data. The green bars represent no palpability whatsoever, the small red components represent abnormal or unexpected feel to the product, and the blue bars represent normal. And see, in and around the time of injection, there's a very small number of individuals with unexpected or abnormal feel. Those were usually typically handled by massage of the area and resolved promptly within two weeks. We do see an increasing amount of non-palpability, which we think corresponds to the absorption of the material that would be expected.

Mass formation, as you recall from the pilot study, it is very important to characterize this. This, in this case, was assessed by the study site staff. There was exactly one episode of mass formation, and I can personally attest to that fact, that that was a mucocele and it was drained with a needle and resolved promptly.

Lastly, we've been looking at the retreatment issues, and we wanted to understand whether or not reinjection was a problem. In this case, the injecting physician was asked if it was difficult to reinject the patient the second time and why was it difficult?

Ninety-three patients underwent reinjection in the study. Two of those patients were noted to have some difficulties with reinjection by the injecting doctor, and in both cases they felt that was due to the presence of dermal filler material and not due to scar fibrosis, et cetera.

So to sum up these lip safety assessments, texture and firmness in most cases was mild in character and lasted less than four weeks.

For lip asymmetry, there were 16 cases that were severe. Most of them resolved in four weeks. Most importantly, all subjects who had a severe rating of lip asymmetry gave themselves a favorable GAIS score.

Palpability was essentially normal for almost all subjects. There were very few unexpected or abnormal palpabilities, and they seemed to resolve with massage.

The rest of the findings, movement, function, sensation, mass

formation, ease of reinjection, were all basically unremarkable.

So after this big body of safety data, how do we understand whether or not this represents an appropriate level of safety for the procedure that's being done?

One of the ways we can do that is look at those proportions of subjects with problems or issues or safety findings and whether or not they were satisfied by their Global Aesthetic Improvement Scores and/or by their willingness to undergo reinjections. We looked at this in the three different components.

For those individuals who had a moderate or severe treatment emergent adverse event, looking at their GAIS scores, almost all, 97%, gave themselves a favorable GAIS score at two weeks, despite having one of those adverse events. Did they have reinjection or not? Recall that the total proportion of individuals in the study who underwent reinjection is 80% or retreatment. That proportion is very similar in this group of individuals who had a moderate or severe treatment emergent adverse event. So they were very willing to undergo reinjection, similar to the rest of the population.

Looking at the diary entries, splitting off those individuals who had affected daily activities or a disabling diary entry, similarly their GAIS score in 97% cases was favorable, and their retreatment rate was almost the same as the general population, at 70%.

Lastly, looking at those subjects who had any abnormality in

their lip safety assessments, similar results, 99% of those individuals gave themselves a favorable GAIS score, and 77% or a very similar proportion to the whole study underwent retreatment.

So, in summary, I think we can say that Restylane for lip augmentation appears to have a very acceptable risk/benefit profile. The treatment emergent adverse events were basically mild and transient in nature in most cases. The diary data collected by the subjects in the subjects' really own words was very comprehensive. Generally, those events were short-lived and reasonably well-tolerated.

Those lip-specific safety assessments we talked about as a very extensive battery of tests, some of those tests were quite stringent, with millimeter differences in single words that can be pronounced, et cetera. Overall, despite that extensive set of testing, the abnormalities were minimal and short-lived.

Lastly, looking at repeat treatment, there is a concern that repeat treatments may be more difficult or more problematic. With respect to adverse events, we saw decreasing frequency, severity, and duration of adverse events in the second treatment versus the first treatment group, and we saw no difficulties or very few difficulties with the reinjection of the material at the second treatment visit.

Now I'd like to turn it over to Dr. Julius Few, who will discuss the treatment of patients of color.

DR. FEW: Thank you, Dr. Smith.

It's an honor for me to be here today. As was mentioned, my name is Julius Few. I'm actually a board-certified plastic surgeon.

By way of disclosure, I am a consultant to Medicis and have served as a consultant for a number of other companies in this industry. I should also note that I was invited to be an investigator for this study and agreed to do so. Unfortunately, I was not able to serve in that capacity because I made an academic change in terms of my affiliation.

Before getting into some of the details of the study and Fitzpatrick Skin Types IV, V, and VI, I'd like to give you a little bit of, at least, clinical background from my perspective.

Even though I'm a plastic surgeon, I was early a doctor in dermal filler use, and really some of that interest was really developed because of a concern dating back to really the release of Restylane around 2003, using hyaluronic acid in skin of color. A number of my colleagues had real concerns that were being voiced at meetings about using dermal fillers and given that this was a product that initially was launched in Scandinavia, that there was a real potential concern.

So I actually did and subsequently published the first study looking at hyaluronic acid in skin of color, and as you can see by the title, really this is a title that would not fly today, but at the time, this was the only approved hyaluronic acid product on the market, and specifically it was

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designed to kind of look at safety and efficacy in skin of color. And I've devoted much of the last decade of my practice to this issue.

In terms of treatment really for darker skin types, the lip indication represents a relatively small minority in terms of an indication. And certainly in my practice, where we're really a specialized center for treatment in darker skin, this probably represents about 5% of the actual dermal filler treatments that I perform in my clinic.

I think it's also important to note that the technical approach and details, which I've published in the initial study, which I think now are considered the standard of care for treating darker skin, really helped to underscore how this is a different subgroup.

And I think, particularly, even looking at aesthetics in terms of the goals and endpoints, you're looking at some differences. As an example, whereas in patients with lighter skin, a typical proportion for upper lip volume to lower lip volume may be closer to one to three, for darker skin or skin of color, it's more commonly one to one. So these are some of the differences that are important, and I'm going to get into why I think this is relevant in terms of the study.

As you look at this cohort of patients, I would say, from a scientific standpoint, this represents a relatively small number, but in terms of this indication, it's actually really a large number. And looking at my experience going back really over about the last decade, I have personally

probably only treated about three patients with Type VI skin for lip enhancement, and all three were related to traumatic loss that I was restoring volume to.

I think, in terms of the absolute numbers, you can see, this represents roughly 24% of the total group number, and in particular, 31 subjects were randomized into initial treatment with Restylane as compared to 10 randomized into the no treatment group. Thirty-nine received a single treatment with Restylane. Thirty-one were at baseline. Eight of the original 10 no treatment subjects were treated at six months for their first treatment. Twenty-two received a second treatment at six months.

And really looking at the effectiveness data for eight weeks, the proportion of MLFS and GAIS responders was truly consistent with the overall larger study.

And as you can see, there's a very tight correlation, looking at the Restylane treatment group and the no treatment group, in regards to the proportion of responders at eight weeks, according to a blinded evaluator for the MLFS.

And, again, looking at the subject GAIS responder analysis at eight weeks, there's once again a very tight correlation, 100%, as you can see here by this graph, as compared to roughly 98% in the general group.

And, again, looking at the investigator GAIS responder analysis, it's once again very tightly correlated in terms of both the blinded assessment

and looking at the more general study group.

So really the differences in portions of MLFS responders between the Restylane and no treatment subjects in darker skin types, at eight weeks, was statistically significant for the upper and the lower lip combined, with a p-value of less than .001. And, again, this was similar to the larger study group.

The incidence of TEAEs both in the first and the second wave of treatment with Restylane was again very similar, and there were no treatment -- and in the no treatment group there were three subjects TEAEs.

In terms of the types of adverse events that were seen in this select group, they were exactly the same in terms of just the overall frequency. And you can see in the list here, which was nicely presented already by Dr. Smith.

And as we look at the breakdown of AEs, I think the one thing that's worth noting is that really all of the AEs, in terms of percentages, were roughly the same as compared to the more general study group, with the exception of swelling. Swelling was higher in this subgroup. And it's important to note that while the swelling incidence overall was higher, the degree of swelling was rated as less severe compared to the more general group. And, again, in the second treatment, you can see as well, the swelling is higher, but again was considered much milder as compared to the general group.

So in terms of safety summary, the most important thing, which, again, these were issues that were raised almost 10 years ago, there have been no reported keloid scars or dyspigmentation events in this study, and to my knowledge, in the world literature, there have been no keloids or scars as a result of hyaluronic acid injection, period.

Subjects with Fitzpatrick Skin Types IV and V appear to have similar adverse event profiles as compared to the total study population. And in terms of the data looking at safety and efficacy for darker skin types in the nasolabial fold, this dataset certainly is consistent with even the larger studies looking at the nasolabial fold and hyaluronic acid use.

Restylane, in summary, is an effective treatment option for darker Fitzpatrick skin types, for submucosal implantation in the lip for the primary purpose of augmentation, and the safety profile in this group is truly acceptable and consistent with the overall study population.

Now I'd like to ask Dr. Lawrence to come back up to finish the presentation.

DR. LAWRENCE: Thank you very much, Dr. Few, and thank you, Panel members, for enduring our very comprehensive presentation this morning.

One of the questions that the Agency has posed to the Panel is related to post-approval studies, and I think we've already had a presentation from the ODE. Certainly Medicis is fully committed to working closely with

the Agency on any post-approval studies, as we discussed with them.

I think one of the important things to note is that we were not actually asked previous to the submission, or even post-submission, to provide any proposed studies, just so that that's clear.

I think also, as the Panel discusses and considers these questions, it is important to have a few points of consideration just to consider. One, this is a very widely used product that has been on the market for over 15 years worldwide and over seven years in the United States, a very lengthy worldwide experience. Multiple millions of patients have been treated with no significant signals other than those that we already have discussed this morning.

It is one of the most extensively studied dermal fillers, both from the standpoint of clinical studies and publications, and again with no significant unique adverse events, although certainly adverse events have been reported and we include those in our studies.

Also, as part of our routine pharmacovigilance responsibilities, which I have as part of my job at the company, we review on an annual basis and update the instructions for use, or IFU package insert, frequently, based on our review not only of U.S. adverse events, but most importantly worldwide adverse events, utilizing our interactions with our partner, Q-Med.

And, finally, it is important to note that this is a non-permanent implant. This is a device that is implanted and resorbed over time by the

body's normal physiologic mechanisms. Hyaluronic acid is a normal component of the body.

Also, if it does need to be removed, it can be removed easily, utilizing hyaluronidase, something that is used not frequently but is occasionally by physicians who choose to remove it at the patient or their decision.

Three of the specific areas. One of them is the evaluation of patients with skin of color. I think Dr. Few had done an excellent job of reviewing his experience, which is quite extensive, regarding patients with skin of color. One of the challenges with any, I think, post-marketing study in this particular indication, as he alluded to, is the fact that many of these patients, especially with the darker skin tones, frequently do not seek lip augmentation. So, again, I think that's just something to consider.

Certainly the issue of younger patients is one that I think needs to be discussed. Certainly, again, this is a not-permanent implant. It also is something -- lip augmentation is frequently chosen on an as-needed basis rather than an ongoing implant, such as something like a breast implant, which is done pretty much a commitment for life.

And then, finally, certainly long-term safety, I would point out that we have a large and extensive database already existing, with the ongoing MAUDE database and then, most importantly, with the significant published literature with all HA and then specifically with lip augmentation.

Let me then just overall summarize what we've heard this morning. We are very proud, I think, of the study and the data that we have collected. We have been very sensitive to requests both coming out of a panel that the FDA sponsored in 2009, as well as a consensus conference from several of the leading societies, which I had the privilege of participating in last year and the year before.

And I think we are really very seriously committed to addressing some of those needs for additional carefully controlled effectiveness and safety data, not only focusing on a quantitative effectiveness, but also how patients are resolving and really feeling that they have achieved the desired aesthetic effect.

Based on that, the data that we presented this morning, we believe, is very robust from an efficacy standpoint. It is highly statistically significant at all time points, by all evaluators and in all effectiveness measures. Also, there is an aesthetically meaningful result in the vast majority of patients at all time points and a high level of patient satisfaction.

Obviously of equal importance, we have done a very comprehensive assessment of safety in this unique indication. Most of the adverse events were generally mild and transient. Even in those patients that had a severe or affecting their activities of daily living, the vast majority of patients, over 80%, chose to have retreatment. I think that is a patient's own assessment of the risk/benefit.

There is importantly, from our special study assessing the lip, which was something that both the Agency and the consensus panel asked for, that there is no evidence of functional impairment in the patients, and repeat treatment does not pose any additional risk.

We believe that this is a favorable risk/benefit assessment. Again, this is a very highly effective device. There's a high level of aesthetic satisfaction as measured by the patients, and about 80% of the eligible patients chose to receive retreatment. It is important to note that about seven of those that chose not to be retreated did so because they already had a satisfactory result.

Even in those patients who did experience events that affected their daily activities, or even the most severe as disabling, similar to the overall population, did in fact make the decision to continue to receive retreatment, I think, again making their own assessment of risk/benefit.

I think it's also important to understand, because many of you may be asking, why are we doing this, well, I think it's very important. We are very committed at Medicis that we only commit to providing promotional activities related to labeled indications. We are very, very proud of being compliant as a company and take our obligations very seriously.

I think, though, in respect to the Panel request and I think also requests of other professional societies, we believe that the broadening indication to include lip augmentation does allow us to provide, and

importantly provides to both physicians and patients, very important safety and effectiveness information, so that both patients and physicians can make an informed decision on whether or not this an appropriate procedure for them and what their expectations might be.

And I think also of equal importance, it will then permit us to undergo the ability to train physicians in the proper use of this device in this indication to ensure that patients are treated appropriately, evaluated appropriately and assessed appropriately.

Therefore, based on the data that have presented this morning, Medicis believes that there is a reasonable assurance that Restylane is safe and effective for the requested expanded indication of submucosal implantation for lip augmentation. We believe that the benefits of Restylane for submucosal implantation for lip augmentation outweigh the risks.

Thank you very much for your kind attention, and I will now be happy to answer, on my behalf or on the behalf of our presenters, any questions that the Panel may have.

DR. GALANDIUK: Thank you, Dr. Lawrence. And I'd like to thank the Sponsor's representatives for their presentation.

Does anyone on the Panel have a brief clarifying question for the Sponsor? And please remember that the Panel may also ask the Sponsor questions during this afternoon's Panel deliberation. Yes.

DR. LAWRENCE: Yes, Dr. Burke.

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DR. BURKE: I'm Dr. Karen Burke, and I have one question and it's about the no treatment group. They had injections of saline?

DR. LAWRENCE: No, no, they did not receive any injections. Actually, as Ms. Lin alluded to, we felt that, given the fact that there are no approved dermal fillers and that we felt it was unethical to actually inject a device, or something like saline, that would not really benefit the patients long term, we felt that it was inappropriate to actually inject or do a sham treatment. So, in fact, working closely with the Agency, we, in fact, chose a no treatment arm, which just gave us the controllability.

Also, the way the study was designed with a very strict criteria for the blinded evaluator, we felt that that would also address it. But those patients did not receive any sham treatment.

DR. BURKE: Could you just state again why you think that 36 to 38% of those people felt they had a response?

DR. LAWRENCE: Certainly, in aesthetic studies, we do see a background noise of about 30%, generally. I think also it's important to note how the rating was done. The patient is evaluated at week 8 and subsequently by the blinded evaluator, without any knowledge of the baseline severity. So it is actually compared back to a different physician's baseline rating. So there may be some chance for some disagreement on that, although I still think the data are quite robust.

DR. GALANDIUK: Dr. Newburger.

DR. LAWRENCE: Yes, Dr. Newburger.

DR. NEWBURGER: Hi. Could you tell me where all the study centers were?

DR. LAWRENCE: Yes. I would actually like Ms. Lin to address that. She has that information on the study centers, please.

MS. LIN: We do have 12 study centers, and the 12 PIs are Dr. David Bank, Dr. Fredric Brandt, Dr. Sue Ellen Cox, Dr. Lisa Donofrio, and Dr. Jeff Dover, Dr. Rick Glogau, Dr. Steven Grekin, Dr. Mark Nestor, Dr. Ava Shamban, Dr. Stacy Smith, Dr. Daniel Stewart, and Dr. Robert Weiss.

DR. NEWBURGER: So then the study centers were basically clustered in the coastal areas, with the exception of Chicago; is that correct?

MS. LIN: I agree, yes.

DR. GALANDIUK: Dr. Halabi.

DR. HALABI: Yes, I would like to clarify on the primary endpoint. So your primary endpoint was pre-specified as an increase at eight weeks from baseline.

Did you observe that for all the 180 patients at eight weeks, or did you have any missing data?

DR. LAWRENCE: I'm sorry, could you clarify the question a little bit, please?

DR. HALABI: Yeah, did you have a measurement, an MLFS

measurement, on every patient at eight weeks or not?

DR. LAWRENCE: Yes, yes, we did. Oh, I'm sorry. Sorry. This is Dr. Stacy Woodard, who is our statistician.

DR. WOODARD: Yeah, hi, I'm Stacy Woodard. I'm a statistician with Quintiles, which is a contract research organization which did the statistical analysis for this study, and I'm also a consultant for Medicis.

So at eight weeks there were 13 patients in the Restylane group and 5 patients in the no treatment group that did not have MLFS assessment by the blinded evaluator at eight weeks. For the primary efficacy analysis, we imputed that data using a hot-deck method. And I'll just clarify for people who may not understand what that is.

So basically we take the patients who were missing the data, we match them with patients who did have complete data at week 8, based on their treatment, their lip that was treated and the baseline MLFS assessment. So we take the missing data from the subjects, we match them with a pool of patients who have those same three characteristics, we randomly select one of those patients and take the eight-week MLFS assessment for that donor patient and use that as an imputation for the missing patient.

DR. GALANDIUK: Dr. Miller.

DR. MILLER: I have a couple of questions just about the technique that was used. All of the patients had the same technique, it was a

submucosal injection, and there was no focal injections around the Cupid's bow or around the lower vermilion, things like?

DR. LAWRENCE: I would actually like to ask if one of our treating investigators might wish to comment on the technique that was used. Dr. Weiss, would you be willing to comment on that, please? Thank you.

DR. WEISS: Yeah, we had the option of using the technique that we used commonly in clinical practice. Most people use a technique where the needle is first threaded in the submucosal area the length of the half-inch needle and then, as it's withdrawn, the hyaluronic acid is injected. Some people use the push-forward technique, where they start the needle in and push forward, and some do a serial puncture. In my site, we consistently used the technique where we threaded the needle and then withdrew, and that technique works best for us.

DR. SMITH: Hi. Stacy Smith.

One of my concerns about your question was, perhaps were you asking, were there injections outside the vermilion, say, to enhance the philtrum and Cupid's bow?

DR. MILLER: Yeah.

DR. SMITH: And no, there were instructions to inject, as Dr. Weiss indicated, along the vermilion border. You described what's called retrograde linear threading, it was that; antegrade linear threading, where

the material is advanced in front of the needle; and serial puncture, again, within the area of the vermilion, to enhance specific areas. But no philtrum or Cupid's bow type of enhance was performed.

DR. MILLER: Okay, another question. It looked like there was up to five cc's injected in some patients, but your recommended dose per session was 1.5 cc's. Did some patients have multiple sessions or did some investigators go beyond the recommended dose for the study? Just explain that.

DR. LAWRENCE: I would like Ms. Lin, who actually conducted the study, to make a comment on that, if she would, please.

MS. LIN: There were actually two criteria for treatment there. One, it's softer recommendation for 1.5 mL per lip per treatment session there. And another goal is to treat the patients to the optimal correction. And, again, optimal correction is defined as best results agreed by patient and the physician. So the physician will use the dermal filler volume needed to reach that optimal correction.

DR. MILLER: Okay.

MS. LIN: And this is added into FDA's recommendation or requirement.

DR. GALANDIUK: And please remember, also we'll have additional opportunity to go deeper into these questions this afternoon.

Dr. McGrath.

DR. MCGRATH: Yeah, I don't know which one of you to direct this to, but I don't understand the touch-ups. You have a beautifully described study with all of these different interventions and photos, and yet somewhere in there there's something going on called touch-ups. And I don't understand how often they're happening and when they're happening.

And in a sense, aren't they second treatments? I mean, you're talking about second treatments at 24 weeks, but I would think that in some cases, if you're doing touch-ups, those are second treatments. So can you just sort of elaborate on what's going on with this? It seems like a little bit of a confused piece in the study.

DR. LAWRENCE: Yeah, I apologize for that confusion. I'll ask Ms. Lin to specifically address that point.

MS. LIN: That is a wonderful question here. So we have two, you know, terms we use, treatment and touch-up, there. So while we talk about treatment, we talk about baseline treatment or month six treatment, and the touch-up refers to that touch-up done two weeks after the treatment. Due to the treatment of the lips area, sometimes you would see swelling and you really don't know whether you achieved the optimal correction or not, after all the bruising and swellings are gone, right?

So after two weeks of the patient treatment there, and the patient will come back to the visit and the physicians and the patients will visit and decide if they have achieved the optimal correction or not. And if

they decided they could use more product to achieve optimal correction, they will do the touch-up. Otherwise they will not do the touch-up.

DR. MCGRATH: Thanks.

DR. GALANDIUK: Dr. Leitch.

DR. LEITCH: It seems like the second treatment dose was always a smaller dose than the first. Not touch-up, but second treatment.

DR. LAWRENCE: Yes, that is correct. In general, it was less, that is true.

DR. LEITCH: And with respect to sort of this five-cc question, getting to five cc's, did that occur in the first treatment or a combination of first and touch-up treatments? How are you counting the five cc's?

DR. LAWRENCE: I would have to defer to Ms. Lin on the specific data of that because it's probably a combination thereof. The question is, how do we obtain this maximum of five cc's in some patients?

MS. LIN: First of all, let me answer the question of why the volume used is less for the six-month treatment. The main reason is because the majority of the patients have still maintained the efficacy at month six there. So you know, you use less volume to achieve back to the optimal correction. I hope this is making sense there.

For the five-cc patients there, we will look at the data and give you the detailed information hopefully by this afternoon.

DR. GALANDIUK: We'll have one more question before our

break.

Ms. Mattivi.

MS. MATTIVI: Kris Mattivi, I'm the Consumer Representative.

DR. LAWRENCE: Yes.

MS. MATTIVI: On the Global Aesthetic Improvement Scale, obviously there was a high degree of patient satisfaction. What was the distribution of responses for the non-responders?

DR. LAWRENCE: Do we have the data on non-responders and their GAIS? I'm afraid we don't. If you'd like, we can certainly try and obtain those data and provide it to you later, if possible.

DR. GALANDIUK: Dr. Burke, you had one additional question?

DR. LAWRENCE: Yes, Dr. Burke?

DR. BURKE: I just had one brief question. When you say 1.5 cc's per lip, that means 1.5 cc's for the upper lip and 1.5 cc's for the lower lip?

DR. LAWRENCE: That is correct, yes. Any other questions?

DR. GALANDIUK: Okay. Sorry, Dr. Mount.

DR. MOUNT: Del Mount.

I have a question about your study populations and how they were actually selected to be enrolled in your study. Were they patients that came in specifically to the centers with complaints of lip fullness issues, or were they selected and they were visiting for other purposes and asked to participate in the study?

And then the last question, this big question is, if they did not choose to be in the study, were there issues or were their concerns about lip augmentation addressed and how were they addressed?

DR. LAWRENCE: Perhaps I'll first ask one of our treating investigators, Dr. Smith maybe, to comment on how, at least at his site, the patients were selected.

DR. SMITH: Stacy Smith again.

So the question basically is how patients were recruited for the study?

DR. MOUNT: Yes, and if they were recruited through your office, coming in with complaints of lips that needed augmentation, in their opinion, but they didn't want to sign up for the study, what happened to that group of individuals?

DR. SMITH: Yes. In our office there are daily requests for lip augmentation. When there's a study, we put out information about a study and subjects -- potential subjects express interest and they are given information to potentially participate in the study. So yes, they are interested in lip augmentation and then find out about the study.

In other offices, where there may be more and more cosmetic patients coming in on a day-to-day basis, some of them may be directed to the study when they're already requesting it.

In our office, if someone doesn't want to be in the study but

still would ask for lip augmentation, we would gladly grant that in a more typical cash service basis like most physicians would.

Does that answer --

DR. MOUNT: Yeah. And for those that -- so the selection criteria to actually be in the study, that decision was made by the individual investigator or were there certain criteria besides being, you know, lip volume 1 or MLFS 1 patient? Were there other criteria that were used for selection of your patients to be in the study, besides just having lack of lip fullness?

DR. SMITH: There's always other considerations, and typically it's really about a potential subject's willingness to participate in a study, and that's a whole different component. There are lots of people who would like to have cosmetic procedures done, but there are only some who will tolerate, if you will, some of the more rigors of being in a research study.

So if some patients want lip augmentation but they don't want to come back every week to have their picture taken and so forth, they're probably not going to consent to be in a study.

So I would say the basic criteria would be to look at, along with having the appropriate physical findings and the desire, is the ability to cooperate with the study, if you will, along with some other minor inclusion/exclusion criteria that are listed in the protocol.

DR. LAWRENCE: And I'll ask Dr. Weiss to comment what his

experiences were.

DR. WEISS: Just a brief comment. We have a very busy office and with five providers. We put up a little IRB-approved notification in the waiting room and, you know, there may be 120 patients in our office in a single day. So the recruitment is from patients coming in to the office for perhaps other reasons. Most of the patients, in my experience, had a complaint of "I have no lips" as really their primary motivation to be in the study.

And I had one patient in particular -- because I would always go in the room and say, "Well, how are things going?" when I'd see them and follow up for the touch-up treatment -- and I had one in particular who said, "You know, what's happened now is that I realize I used to burn my mouth all the time with my Starbucks or whatever, and now I can actually tell that it's hot."

So it was like wow, a functional improvement. I learned a lot from that statement, and she wasn't the only one to tell me that. I tried to get her down here today to testify, but she travels a lot and it didn't match her schedule, but I would like to have you hear from her. So those are the typical issues.

DR. MOUNT: So basically all comers that would come in your office seeking to be in the study and promising to fulfill the criteria and meeting the criteria physically would be enrolled in a study? There's not an

additional selection bias that could be introduced by the clinician to either be in or out of the study?

DR. WEISS: I mean, I looked at that MLFS, and if they had like -- we prefer people with almost no lips in there to have the lowest grade. But I don't think there was any specific or additional bias.

DR. LAWRENCE: And we do have the answer to your question. I apologize for not knowing it at hand. In fact, all of the patients who were treated, even if they did not -- were not rated as a responder, which is that one-grade improvement, did still feel that they had improvement rated by the GAIS, about 99-point-some percent. None of the patients in the no treatment group had a GAIS that was considered positive.

So really there was a very strong correlation that having treatment did result in a rating of improvement, at least initially after that first evaluation of the GAIS at two weeks.

Some of those patients, about -- in the case of the blinded evaluator, some 8 or 10% of those would not have been rated as a full one-grade improvement in the MLFS scale, and that in part reflects the fact that you have a scale that may require a greater volume and perhaps a greater correction than the patient was really seeking. So I think it reflects their satisfaction to optimal treatment versus a requirement to actually force them to have a one-grade improvement.

MS. MATTIVI: So were there any -- in the responder group,

were there any that had a GAIS score of worse?

DR. LAWRENCE: Were there any lower or negative? Yes, Ms. Lin?

MS. LIN: Yes, we do, and out of 180 patients, we have seven patients, and during all of the assessment, nine events of the GAIS decreased, and six of them are in the treatment group and one of them in the no treatment group. For overall in the treatment group, there are six patients, seven, eight events, eight time points that GAIS decreased.

DR. GALANDIUK: Dr. Leitch.

DR. LEITCH: Of the proportion at the six months who said -- I think it was like 75% or something that were still satisfied -- what proportion of them had touch-ups versus the proportion that had touch-ups in the not continuing to be satisfied?

DR. LAWRENCE: That we don't have at our fingertips, but we can certainly look into that. That's an excellent question, Doctor, and we'll try and get that back to you later this afternoon.

DR. LEITCH: Okay.

DR. GALANDIUK: We'll now take a 15-minute break. And Panel members, please do not discuss the meeting topic during the break either amongst yourselves or with any members of the audience. We'll reconvene at 10:25. Thank you.

(Off the record.)

(On the record.)

DR. GALANDIUK: It is now 10:25 and I would like to call this meeting back to order.

FDA will now give their presentation on this issue. Dr. Durfor, you will have 90 minutes.

DR. DURFOR: Good morning. My name is Charles Durfor, and I am leading off the FDA presentation. Today we're here to talk about Panel Track Supplement 51 to PMA P040024, Restylane injectable gel, by Medicis.

Restylane injectable gel is a chemically cross-linked hyaluronic acid, purified from a gram-positive streptococcus. It's suspended in physiological buffer at about 20 milligrams per mL and the fill size is there and it's also co-packaged with a sterile syringe, needles.

In March 25th of 2005, the PMA was approved for mid-to-deep dermal implantation for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. And as you know, today we are here to discuss an expanded indication, submucosal injection for lip augmentation.

Because this particular panel track supplement did not include a change in product manufacture or specification, the supplement did not contain any manufacturing or preclinical data. Instead, the data that have been previously presented in this PMA are believed to be sufficient to support any consideration of a new proposed indication for use.

So to give you an idea of the FDA presentation that you're

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going to hear, Janette Alexander will follow me as the clinical reviewer. Alvin Van Orden will then give you the FDA's statistical perspective. Nasrin Mirsaidi will then give you information on what we have learned about the product in our voluntary post-market reporting because, as you've heard, the product has been commercially available for several years and it's important to know what sort of adverse events have been reported to FDA for off-label use. And finally Megan Gatski will give you the post-market considerations for such a product.

With that I'd like to introduce Dr. Janette Alexander.

DR. ALEXANDER: Good morning. I'm Janette Alexander. I'm the plastic surgeon reviewer at the Plastic Surgery Branch of CDRH, and I'll present the clinical overview for you today.

Restylane was previously approved in 2005 by Medicis for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds. Medicis has now completed studies in support of a request for an expanded indication in lip augmentation.

Restylane for lip augmentation is presented for Panel discussion because lip augmentation is a first-of-a-kind indication for use. It is to be administered in the submucosal plane as opposed to the dermal plane. A pivotal study was performed to evaluate the safety and effectiveness in the augmentation of soft tissue fullness of the lips.

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There were two pilot studies performed. The first is a U.S. study of 20 subjects. Safety data was collected by diary for 14 days, and investigator visits were performed at 72 hours and 2, 6, 12, and 24 weeks after treatment, with evaluation at 12 weeks for global improvement.

Total mean volume of Restylane injected across both lips was 1.69 cc's per subject. Seven treatment emergent adverse events were experienced by four Restylane-treated subjects. Two subjects had one event each of mild bruising that was considered to be caused by the injection procedure, but these were events that were anticipated to occur as a result of the route of administration. Adverse outcomes in patient diaries were similar to those reported in the pivotal study.

The second pilot study was done in Canada and used the Medicis Lip Fullness Scale, developed by Medicis, that is used in the pivotal study.

Total mean volume of Restylane injected across both lips was 1.96 cc's per subject. There were eight adverse events in six subjects during the study, none of which were judged to be device related. One patient had an anxiety attack related to the presence of Restylane in the lips and resulted in hyaluronidase administration for removal. She had a history of anxiety, which emphasizes the need for careful patient selection.

Study MA-1300-15 was a randomized, evaluator-blinded, no-treatment controlled study of the effectiveness and safety of Restylane in the

augmentation of soft tissue fullness of the lips. The no treatment patients were treated with Restylane at 24 weeks.

The primary effectiveness endpoint was a test of whether Restylane was more effective than no treatment, as determined by the blinded evaluator assessment of lip fullness at eight weeks after treatment, as compared to baseline lip fullness assessments performed by the treating investigator.

Separate upper and lower lip evaluations were performed as co-primary endpoints using the validated five-grade Medicis Lip Fullness Scale. Treatment success was defined as at least a one-grade increase in lip fullness score for both upper and lower lips combined.

Secondary endpoints included blinded evaluator assessment at subsequent weeks; treating investigator assessment at all time points; photographic reviewer assessment at all time points and all sites; subject assessment and treating investigator global assessment at all time points; correlation between lip fullness score and global assessment scores by the treating investigator and to the subject global assessment; agreement in proportion of responders between lip fullness scale and global assessment for the treating investigator; and agreement between treating investigator, blinded evaluator, and independent photograph reviewer assessments using the lip fullness scale.

A separate scale was used for upper and lower lips. A

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validation study was done using 85 photos and five evaluators, with intra-rater agreement of .81 and inter-rater agreement between .6 and .81. When rated with live subjects versus photos, reliability was between .61 and .68. This study provided support that a one-point difference was clinically detectable.

The primary safety objective was to identify the incidence of all adverse events, including subject adverse outcomes reported during the first 14 days after treatment in a subject diary, as well as safety assessments and adverse events by the treating investigator at a 72-hour visit and visits at 2, 4, 8, 12, 16, 20, and 24 weeks after the last treatment and 2 and 4 weeks after the week 24 retreatment.

Secondary safety evaluations included lip assessments for texture, firmness, symmetry, product palpability, mass formation, and functional assessments, including lip movement and function and sensation. These secondary assessments were made by a designated study staff member, who was different than the investigators, in order to maintain blinding.

There were 180 patients randomized in a three-to-one ratio, resulting in 135 patients treated with Restylane at the onset of the study and a no-treatment control group of 45 patients that were offered treatment at 24 weeks and then followed for four weeks to collect safety data.

Subjects were enrolled at 12 investigational centers by 12

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investigators. To maintain masking, all baseline assessments, including lip fullness scale scoring, were performed by the treating investigator. Patients were evaluated at 72 hours and 2, 4, 8, 12, 16, 20, and 24 weeks after the last treatment or no treatment. Touch-up treatments were provided at two weeks post-treatment if required to achieve optimal correction.

Subjects completed a 14-day post-treatment diary after each injection. The treating investigator assessed safety outcomes at each visit, and a study staff member evaluated patients for abnormal lip texture, lip firmness, and lip symmetry, as well as abnormal lip movement, function, and sensation, and mass formation at each study visit.

The treating investigator performed lip fullness scale scores and Global Aesthetic Improvement Scale evaluations after each visit. The blinded evaluator determined lip fullness scores at weeks 8, 12, 16, 20, and 24 after the last treatment. Subjects performed a global assessment after each visit and photographic records were collected after each visit.

All subjects, both treatment and control, were offered Restylane injections at the week 24 visit. Clinical visits after this injection included monitoring safety outcomes at 72 hours, as well as weeks 2 and 4 after the last treatment, in a manner consistent with the initial treatment protocol. Touch-up treatments were provided at two weeks, if required.

The mean age was 47.6 years, with a range of 18 to 65. Most subjects were female and white. One patient was male. Of note, there were

four patients under 22 years of age. Younger patients may be a group interested in lip augmentation and may receive more treatments over time than older patients.

We will ask you to consider the implications of treatment of younger patients in your discussion.

There were 38 Fitzpatrick IV and 3 Fitzpatrick V patients in the study. The treatment group included 31 Fitzpatrick IV and V, and 10 of the 41 were in the no-treatment control group. The Sponsor has performed a previous study of use of Restylane in nasolabial folds in 150 Fitzpatrick IV through VI patients.

We will ask you to discuss the applicability of the Sponsor's previous nasolabial fold study to use in the lip for this population.

Nineteen patients were lost to follow-up or withdrew consent, and six of the no-treatment patients withdrew, resulting in 155 patients completing the study.

The mean volume injected in the initial treatment and touch-up was 2.9 cc's per patient, with a range of .6 to 5.6 cc's. Device implantation was achieved by submucosal injection in all patients. The majority of subjects received a combination of injection methods, such as linear retrograde, linear antegrade, and serial puncture. Most patients received an anesthetic, either topical or injected locally or regionally or both, although fewer patients received injected anesthetic with subsequent treatments.

In the Restylane group, the blinded evaluator's assessment at week 8 showed 95% of the subjects to be upper lip responders and 94% of the subjects to be lower lip responders. For upper and lower lips combined, 93% of the subjects responded to Restylane at week 8 as evaluated by the blinded evaluator.

In the no-treatment group, 29% of the subjects had blinded evaluator lip fullness score ratings that were at least one grade higher than baseline and were considered responders for both upper and lower lips combined.

The study met the pre-specified primary effectiveness criterion for the difference in proportion of responders for upper and lower lips, separately and combined.

A blinded evaluator determination of lip fullness scale score was also performed at weeks 12, 16, 20, and 24, as well as 2 and 4 weeks after the week 24 retreatment. The difference in the proportion of Restylane and no-treatment responders was significant at all time points when upper and lower lips were evaluated separately or combined.

Independent photographic reviewer's assessment of lip fullness scale score was performed after study completion, using photographic images collected from all sites during the study. The difference in the proportion of Restylane and no-treatment lip fullness scale responders was significant at all time points when upper and lower lips were evaluated separately or

combined.

There was poor agreement between the treating investigators, the blinded investigators, and the photographic evaluators. This will be discussed in greater detail by our statistician later in the presentation.

The maximum recommended volume per patient for each treatment was three cc's, based on pilot studies' mean volumes of 1.69 and 1.96 cc's per patient. The average volume for initial injection was 2.39 cc's per patient. This is broken down to 1.28 cc's for the upper lip and 1.11 cc for the lower lip, with touch-up volumes for the upper lip of .53 and .41 for the lower lip.

Forty-four patients received volumes higher than the recommended maximum at the initial injection, and another 32 received augmentation to bring them above the recommended maximum at the two-week touch-up, for combined initial injection and touch-up.

This graph is presented with adverse events seen in the first 14 days by volume at the initial injection. It appears that moderate and severe adverse events are related to higher injected volumes.

This graph shows that the incidence of adverse events with the touch-up injection at two weeks was lower and milder than after the initial injection, but was still related to the volume of the injection.

Increased incidence in severity with increased volume is also true for the combined volumes given in the initial plus touch-up injections,

although the incidence of severe events remains low.

You will be asked to discuss the relationship between increased volume and incidence and severity of adverse events, and to comment on recommended volume maximums or guidelines.

Safety endpoints were specific anticipated events, such as bruising, redness, swelling, pain, tenderness, and itching, were reported during the first 14 days after each treatment in a subject diary.

Lip safety assessments and treatment emergent adverse events were evaluated by treating investigators at each scheduled visit, and lip texture, firmness, symmetry, product palpability, mass formation, lip movement and function, and lip sensation were evaluated by a designated study staff member.

I'll go over the specific functional and sensory assessments. About 23% of subjects exhibited mild abnormal lip firmness. One subject exhibited moderate lip firmness, which resolved in less than two weeks. No subjects experienced severe abnormal upper or lower lip firmness at any time point.

Severe lip asymmetry occurred in 16 out of 180 patients, approximately 9% of the patients, at some time point during the study, and generally the severe asymmetry resolved in four weeks or less. Global assessment scores by the patient at the corresponding or next closest visit indicated that all subjects with severe asymmetry judged themselves as

improved or better. It is interesting that patients did not complain about the asymmetry.

The majority of Restylane subjects experienced a palpable implant through their week 24 visit. Device palpability decreased over time, from 100% of patients after initial treatment to 61% of patients at 24 weeks. The evaluators were asked to assess whether the palpability was expected or unexpected. An unexpected feel of the product was observed in 3% of Restylane-treated patients. Such assessments occurred between the 72-hour post-treatment visit and week 4, and staff member reports of five patients with eight lumps were captured in this category, although no nodules were reported by patients in the patient diary.

One patient was assessed to have mass formation, which developed two weeks after retreatment at 24 weeks, which was described as a small mucocele and required surgical drainage for resolution.

Lip movement was tested by assessing pronunciation of words chosen from the International Phonetic Alphabet's bilabial and labiodental reference words. One subject in the no-treatment group and one subject in the Restylane group at week 24 failed to pronounce all of the words, even though they had passed the test during previous visits. One additional subject in the Restylane group could not pronounce all of the words at the week 4 visit that occurred after retreatment series at week 24.

Lip function was tested by assessing a subject's ability to suck

liquid through a straw. All subjects were able to complete this activity at all time points during the study.

Lip sensation was tested via two methods, the monofilament test, which evaluated a subject's ability to feel the sensation of a small monofilament at three points on the upper lip and three points on the lower lip, and the cotton wisp test, which evaluated a subject's ability to feel the sensation of a cotton wisp at three points on the upper lip and three points on the lower lip. Two patients did not pass this test at a single time point each.

Anticipated adverse events were swelling, redness, bruising, pain, tenderness, and itching. Skin exfoliation was also commonly found. There were 10 patients who developed oral herpes. Three outbreaks were not temporally associated with Restylane injection. Six out of 10 herpes outbreaks were within seven days of injection, and 1 out of 10 occurred at two weeks. Eight of the 10 were treated for the adverse with antiviral treatment after the onset of vesicles, with resolution in 2 to 14 days. Two of the 10 were not treated and had resolution in four to six days. Only one patient received prophylactic antiviral medication, and she did not have an outbreak immediately after injection, although had one three months later.

This graph shows the total number of subjects reporting adverse outcomes. Patients' descriptions of adverse outcomes are none, tolerable, affecting daily activity, and disabling. This represents the first

treatment and touch-up, if provided, and this is the second treatment at 24 weeks with touch-up, if necessary. You can see that a significant number reported outcomes described as affecting daily activity or disabling.

The onset of commonly reported treatment emergent adverse events, which are swelling, redness, bruising, tenderness, typically began within a day of being treated and they were transient in nature.

As seen in the previous slide, 40% of subjects had adverse outcomes that they felt affected their daily activity or were disabling but were short lived. Fifteen percent of the patients experienced adverse events, typically swelling and tenderness, that lasted longer than 15 days. A small number had bruising or pain that lasted longer than two weeks.

To better understand the profile of the product, FDA asked the Sponsor to provide photographic examples from each site of patients with disabling outcomes and patients with typical results. To ensure a complete review of this application, it is appropriate to show you a subset of the photos, included in your Panel pack, that demonstrate the adverse outcomes and ask you to discuss their importance. I'm going to show you slides of patients who had an adverse event that they considered disabling, to show you the spectrum of appearance associated with disabling symptoms and to relate these symptoms to the volumes the patients received.

This patient is presented in both groups with an adverse outcome that is disabling and with a desirable result. She described severe

pain that was disabling for one day. She had initial treatment with 1.5 cc's in the upper lip and 1.2 cc's in the lower lip, with a touch-up at two weeks of .5 cc's in the upper lip and .2 cc's in the lower lip. She returned at 24 weeks for repeat treatment and received .4 cc's in the upper lip and .6 cc's in the lower lip. This shows her result at the conclusion of the study, one month after retreatment.

This patient received one cc in each lip, with a touch-up at two weeks of one cc in each lip. Her adverse outcome was described as bruising, pain, swelling, and tenderness. She considered the severity to be disabling. Note the asymmetry and bruising on the left upper lip. This is a close-up at three days and at the eight-week endpoint.

This patient received 1.4 cc's in the upper lip and 1.6 cc's in the lower lip. Her adverse outcome was swelling, and the severity was disabling. She had repeat treatment and touch-up at 24 weeks, again experiencing disabling swelling.

This patient received 1.9 cc's in each lip, with a touch-up of .2 cc's in each lip. Her adverse outcome was pain and swelling, the severity was disabling, and she refused retreatment due to the pain and the swelling. This shows her appearance at three days and at eight weeks.

This Fitzpatrick V patient had her upper lip only injected with 1.3 cc's. She described her adverse outcome as swelling and the severity as disabling. This shows her outcome at 72 hours and at four weeks. She was

lost to follow-up after four weeks.

The last photo is this patient, who received one cc in each lip without touch-up. Her adverse outcome was severe swelling, which she considered disabling. She declined further treatment as she was very happy with her appearance, and this shows her final appearance at the conclusion of the study.

In summary, the study met its primary endpoints and most of its secondary endpoints. Exact evaluator agreement was poor. There was a wide range of volume injected, and volume did not correlate directly with effectiveness outcomes. Treatment-emergent adverse events were common, but were transient and predominantly mild. However, 40% of patients described events which affected daily living or were disabling. Volume injected does correlate with adverse event impact. There were few Fitzpatrick Type V and no Fitzpatrick Type VI patients represented. Younger patients may be interested in lip augmentation and may potentially receive multiple repeat treatments over many years.

We would appreciate your discussion of the relationship between volume injected and outcome, as well as the adequacy or need for data regarding the augmentation in Fitzpatrick V and VI skin types and in younger patients.

I thank you for your attention.

MR. VAN ORDEN: Hi, my name is Alvin Van Orden, and I will be

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discussing the statistical aspects of this PMA.

The study design has already been discussed in detail, but I will repeat some important highlights, some important parts.

One hundred and eighty subjects were randomized in a 3:1 fashion to either a Restylane or a no-treatment group. The primary endpoint was based on the Medicis Lip Fullness Scale, and to enter into the study an inclusion criterion was that subjects needed to be assessed as having very thin or thin lips. To be a success or a responder, the subjects had to show a one-category improvement at eight weeks. Upper and lower lips were evaluated using slightly different scales, and the study needed to show improvement in both upper and lower lips in order for the study to be considered a success.

Evaluations of lip fullness were done by three different people or groups of people. The treating investigator made the initial assessment of subjects to decide if subjects should be enrolled in the study and made evaluations at every visit throughout the study.

The blinded evaluator also made live, in-person assessments, and it was pre-specified that the blinded evaluator's assessment would be used for the primary analysis.

The independent photographic reviewers looked at photographs of the subjects at each time point, without knowing which time point it was, and evaluated the subjects on the same MLFS scale. The median

or middle score from the three photographic reviewers was used.

In order to maintain the blinding of the blinded evaluator, the blinded evaluator did not make any evaluations until the week 8 primary time point. As the blinded evaluator did not do any previous evaluations, the blinded evaluator's week 8 assessment was compared to the treating investigator's baseline assessment.

As the treating investigator performed the baseline evaluation before randomization, we assumed that the treating investigator's assessment would be similar to the blinded evaluator's baseline assessment, if he had performed it, because we believed two people seeing the same subject would give the same rating on the MLFS the large majority of the time.

Please also keep in mind that subjects were not blinded. It's unknown if some subjects may have presented their lips differently or behaved differently during the trial because they knew if they had been treated or not.

The primary analysis was a responder analysis, where, again, a responder is someone who has shown a one-point increase. The difference in the responder rates for the upper and lower lips is 58 and 56%, respectively. And looking at subjects that were responders on both upper and lower lips, the difference in responder rates is 64%. All of these differences are highly statistically significant.

This table shows the mean and median changes from baseline at week 8. The median improvement for the Restylane group is two categories, more than was required to be defined as a responder.

In this table we see the responder rates at 8 and 24 weeks for upper and lower lips combined for the three different evaluators: blinded, treating, and independent photographic reviewers. The all-three column shows the subjects that were considered responders by all three of the different evaluators. At eight weeks, just above half of the subjects improved enough to be considered responders by all of the evaluators, and by six months 22% of subjects were considered responders by all evaluators.

We assume that there were no changes in the lips of the subjects in the no-treatment group. So any subjects that were classified by evaluators as responders might be considered false positives. We might also assume that there would be a similar rate of false positives in the evaluators' assessments of subjects in the Restylane group.

There are potential problems then with taking any of the three evaluators' assessments at face value. The blinded evaluators had the highest proportion of subjects that were falsely evaluated as responders. The treating investigator was not blinded and is subject to bias. The photographic reviewers only had 2-D images.

The Panel will be asked which is the best way to evaluate lip fullness, and what is the best estimate of the effectiveness of the Restylane

group when compared to the control?

Next, we will talk about the agreement between different evaluators. One method of assessing agreement is weighted kappa. There are multiple published methods for interpreting weighted kappa values, and this table shows the two most commonly accepted interpretations. Kappa values below 0.4 are considered poor or fair to poor.

As you can see here, the weighted kappa values show that there was borderline fair agreement between the live evaluators and poor agreement between the live evaluators and the photographic reviewers. Evaluators only gave the exact same assessment of lip fullness about half the time.

Also keep in mind that, unlike the photographic reviewers, who are the same for the whole study, different blinded and treating evaluators were at each site and there were significant differences between sites.

Even among photographic reviewers that were seeing the exact same photographs, the level of agreement was low. As you can see, the amount of exact agreement ranged from 27% to 62%.

Given the low levels of agreement between evaluators, the Panel will be asked if a one-point difference on the MLFS scale is clinically meaningful and if there is a better way of assessing lip fullness that might give more consistent results.

We remind the Panel that the Sponsor demonstrated more

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than a one-point difference and the FDA agreed to the use of the MLFS scale. However, comments about clinical meaningfulness and assessment methods will help us design better studies in the future.

A secondary endpoint was the investigator and subject's assessment of improvement. We remind the Panel that this endpoint was not blinded and depends heavily on the ability of the subject or investigator to remember their appearance at least two months previous, so it is not a reliable indicator of effectiveness.

Still, nearly all subjects and investigators reported seeing improvement at week 8. There is some correlation between aesthetic improvement and lip fullness, but a very large increase in lip fullness may not be aesthetically more desirable than a small increase.

Eleven percent of subjects did not complete the study, and missing data was imputed for the primary analysis. Even in a worst-case scenario, where all missing subjects in the Restylane group were imputed as failures and where all missing subjects in the no-treatment group were imputed as successes, there would still be a statistically significant difference in favor of the Restylane group.

At six months, subjects in the Restylane group were offered a second treatment and subjects in the no-treatment group were offered a first treatment. Twenty-three subjects that had not previously dropped out of the study, for other reasons, declined additional treatment. Some of these

subjects declined because they perceived continued efficacy.

However, as the cohort that received a second treatment is a non-randomly selected subset of the total study population, one should be careful in drawing conclusions based on this data, in comparing -- specifically in comparing adverse event rates.

In the IDE the Sponsor proposed limiting the volume of the injection to 1.5 milliliters per lip or three milliliters total. Despite this recommendation, nearly half of subjects received more than the recommended amount. This is an important issue because increased volume does not appear to increase effectiveness, while it does increase safety concerns.

The next two slides attempt show the relationship between volume injected and the improvement in lip fullness as measured by the change from baseline in MLFS.

This plot shows upper lips at week 8 and differentiates between those that received a touch-up injection and those that did not. As you can see, an increase in injection volume does not predict an increase in lip fullness as measured by the blinded evaluator. Subjects with low volumes had high success rates and some high volumes had no improvement.

This plot shows lower lips at 24 weeks and differentiates between baseline MLFS scores of thin and very thin. We looked at a variety of statistical models, and volume injected was not a significant predictor of lip

fullness in any of these models.

Treating investigators injected volume based on the subject's anatomical features and the desired outcome. But if some investigators choose to inject greater volumes than others, it is unclear how much change in the volume injected affects the desired outcome.

The Panel will be asked to comment on the relationship between the volume and effectiveness.

Subjects that were injected with more than the recommended three milliliters were significantly more likely to have either moderate or severe adverse events. The first line shows the percent of subjects that had treatment emergent adverse events within two weeks of the first injection. The second line is based on the total volume injected, including touch-up, and shows the percent of subjects that had any adverse events in the study. As you can see, both were highly statistically significant.

The Panel will be asked to comment on the safety of the investigational device for high-volume injections. The Panel will also be asked if a maximum volume injected should be recommended and what the maximum volume should be.

As can be seen in this table, almost all subjects reported adverse events after injection, and most of these were expected and lasted less than two weeks.

After my presentation, my colleague will present a report of

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adverse events that have been reported during off-label use, such as hyperpigmentation, anaphylactic shock, necrosis, and grape-sized lumps. Even though in this study we did not see any events of necrosis, for example, we estimate that the true percentage of subjects that will experience necrosis and such events is between 0 and 2.12%.

In summary, the primary and secondary endpoints were all highly statistically significant. Lack of agreement between evaluators makes it difficult to estimate just how effective this treatment is. The volume injected is not a significant predictor of effectiveness, but it is a significant predictor of moderate to severe adverse events. Nearly all subjects will experience mild transient adverse events, and some subjects will experience more severe adverse events.

I will now turn the time to Nasrin Mirsaidi, who will discuss the off-label use.

MS. MIRSAIDI: Hello, my name is Nasrin Mirsaidi. I'm one of the MDR reviewers in the Office of Surveillance and Biometrics, and I'll present adverse events reported to FDA regarding the use of Restylane in lip augmentation.

I'll start my presentation with methodology through which the MDRs were searched and captured, and then I'll go over the limitations of data analysis and I'll present the findings in three different sections: one, overall data but all the reports that were received, regardless of the site of

injection, and then the ones was regarding lip augmentation. Some of them were combined with other sites and some were single-site injections. And then I'll finish my presentation with a conclusion.

Our MDR database, called MAUDE, which stands for Manufacturer and User Facility Device Experience, was searched using many different variations of search criteria, but the most effective one that resulted was the one that we used several variations of the brand name Restylane, and that generated 119 reports that were received through the years.

These 119 reports then were individually reviewed and sorted for the ones that mentioned injection into the lips or upper or lower lip or vermilion border. Thirty-seven of them, which is almost over 30% of the reports, were related to injection to the lips, 15 of them as single site, and 22 of them were combined with other sites of injection.

On the limitations of data analysis, as you may know, our MDRs have their own limitations and the analysis of our MDR data should be evaluated in light of its limitations. In the specific analysis we had the following limitations:

First of all, the terms that were used to describe adverse events were ambiguous and not uniform. For example, for lesions that could be granuloma or nodules or abscess, the terms lumps and bumps and lesion and mass was used. Secondly, direct association of adverse events with the injection of the product is not always identified because of the lack of the

accurate information. And then unknown pre-injection local anesthetic use in some reports, and some didn't use local anesthetics. So we are not sure whether the local anesthetic caused the adverse events or Restylane.

Also we had injection of other products at the same time Restylane was injected, like all other types of dermal implants or other products such as Botox. Multiple sites of injection also reported and therefore we didn't -- we couldn't identify whether the adverse event was related directly to the lip injection or other sites that were injected.

And, finally, the relationship between patients' past history of Restylane cannot be identified to the present adverse event because some of them were injected and some of them were not injected in the past. And even those that did not mention anything about the past injection, we were not sure whether the information was missing or the patient actually didn't have the injection in the past.

And now I'll go over the findings and first go over the overall data related to 119 reports.

One hundred and three reports were submitted by manufacturers and 16 by voluntary reporters. Type of events was not correctly marked in all the reports. So when we reviewed individual reports, we corrected the type of events to reflect the actual adverse event. So the corrected type of events were no death, 117 injuries, and two other. And the two other means that they didn't fall into malfunction or into injury reports.

So, for example, one of the reports was just a general complaint about the product and the manufacturer practice, and the other one reported that the injector cut his finger because the syringe broke during injection and cut his finger.

Country of origin was identified in 109 reports as U.S., and 10 of them didn't have country of origin, so we don't know whether they were from outside the U.S. or not. Age was reported in 99 reports and ranged from 28 to 73, and 28 didn't mention any age of the patient. Gender was mentioned in 118 reports, 110 female, 8 male, and 1 unknown.

In this table you will see the number of reports during the years the product has been marketed. Eighty-four of the reports were under Q-Med as manufacturer and 33 was Medicis. Also in this table, 117 reports are the total because two of them did not have the manufacturer's name. And as you notice, in 2010 and 2011, the number of reports received dropped sharply, and we don't have any explanation for that.

This chart shows the top 10 adverse events in total of reports that we received. So the top 10, and as you see, swelling followed by skin discoloration, erythema, and then we have hypersensitivity, and scar and necrosis. And when we are talking about swelling, we're talking about severe swelling. It's not the expected swelling that we see at an expected injection site.

This table shows the 37 reports that indicated injection into the

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lips. Only 15 of them were a single site, and the other ones show variations of the sites beside lips and vermilion border. Since adverse events reported in the multiple site group could potentially be related to injection to other sites and not to the lips, I will present the data analysis into a different section.

For the multiple sites, there were 22 patients, and you will see swelling, again followed by skin discoloration, bruise, allergic reaction, and hypersensitivity and anaphylaxis were four patients. Again, allergic reaction here is severe allergic reaction for which the patient had to go to ER or get admitted to the hospital.

We had vascular accidents and necrosis, hyperpigmentation, erythema, and then in this one, lumps and bumps. And the herpes breakout, I have three patients, but two were confirmed herpes and one didn't mention -- as it confirms it, it puts herpes-like lesions, but the patient's symptoms were treated with antiviral medication.

For the single-site group, 15 patients. And in this group I separated them immediate adverse events, which is immediately after injection or during the first 24 hours, and delayed ones that occurred after 24 hours, up to days, weeks, or months: again, swelling, lumps and bumps, skin discoloration, erythema, allergic reaction, and followed by angioedema, severe angioedema, infection and abscess, vascular accidents and necrosis, broken capillary and granuloma, and desquamation.

As you have noticed, a number of these adverse events are shared between the two groups of multiple and single sites. We have seen severe swelling, lumps and bumps, skin discoloration, infection, broken capillary, angioedema, vascular accidents and necrosis, and severe allergic reaction in both groups.

For the treatment of adverse events, the interventions required for treatment of adverse events varied according to the severity and type of adverse events. Some patients' symptoms required only medication, like a steroid, topical or oral, or intra-lesion injections, oral or IV antibiotics and antihistamines, while others needed a combination of therapies, like medication plus I&D of an abscess or excision of a lesion and biopsy. Some of the patients had to go to ER and get hospitalized. Four of the 22 patients in the multiple-site group and 3 of 15 patients in the single-site group had to be examined in ER and hospitalized.

My conclusion would be the adverse events not reported in clinical studies. We have seen adverse events that are similar to the ones that we saw in clinical studies and the ones that we have not. For example, allergic reaction and swelling was reported in the clinical study, but we have seen severe. The severity of them were not seen in the clinical study. And skin discoloration was not seen. Infection and abscess, vascular accidents and necrosis and scarring was not seen, and severe angioedema. We have also seen many different off-label use of the device, such as molar region,

glabella, lips, and marionette line.

All in all, true incident of adverse events in U.S. cannot be identified through MDRs due to a small number and low quality of reports.

Here I try to emphasize on reporting adverse events, and it's a kind of plea to the healthcare professionals that voluntary reporting of adverse events to FDA, such as filling out a MedWatch form by the healthcare professionals, become crucial in having a stronger set of data. So please report to FDA.

And finally we're hoping that presented MDR data can help the Panel Members to determine the pre-market assessment of approvability and the appropriateness of the post-market approval studies.

Thank you for your attention.

DR. GATSKI: Good morning, distinguished Panel and audience members. My name is Megan Gatski and I'm an epidemiologist and nurse consultant in the Division of Epidemiology, Office of Surveillance and Biometrics. I will be presenting the post-approval study considerations.

Before we talk about post-approval studies, we need to clarify a few things. The discussion of a post-approval study prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective. The plan to conduct a post-approval study does not decrease the threshold of evidence required by FDA for device approval. The pre-market data submitted to the Agency and

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discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate risk/benefit balance.

There are two general principles for post-approval studies. The main objective of conducting post-approval studies is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after pre-market establishment of reasonable evidence of device safety and effectiveness. Post-approval studies should not be used to evaluate unresolved issues from the pre-market phase that are important to the initial establishment of device safety effectiveness.

The specific reasons for conducting post-approval studies are to gather post-market information, including longer-term performance of the device; data on how the device performs in the real world in a broader patient population that is treated by community-based physicians and specialists, as opposed to highly selected patients treated by investigators in clinical trials; evaluation of the effectiveness of training programs for use of devices; evaluation of device performance in subgroups of patients, since clinical trials tend to have limited numbers of patients in certain vulnerable subgroups of the general patient population; monitor adverse events, especially rare adverse events that were not observed in the clinical trials. In addition, post-approval studies can also address any other issues that may be

identified by Panel members based on their expertise.

When designing a post-approval study, the following elements must be included: a fundamental study question or hypothesis, safety endpoints and methods of assessment, acute and chronic effectiveness endpoints and methods of assessment, and specified duration of follow-up.

Until recently, plastic surgeons were concerned with techniques of rejuvenation of aging lips, generally in patients at least 40 years of age. However, over the last decade a younger group of patients has been requesting aesthetic enhancement of the lips. In the year 2010, nearly 1.8 million people had soft tissue filler augmentation, which is a 172% increase since the year 2000.

A younger population of patients under the age of 40 could receive multiple treatments for lip augmentation over a time span of 5, 10, 15 years or longer. We do not know the safety and effectiveness of the device after multiple treatments given over time. A potential post-market question to be addressed is what is the long-term device performance in a younger population receiving multiple treatments over time?

The applicant did not include a discussion of post-market plans in their pre-market submission.

The Panel will be asked to discuss and comment on the appropriateness of the following possible post-market questions: The pre-market device performance data reflects single Restylane treatment sessions

in 172 patients and a repeat Restylane treatment in 93 patients. Please discuss whether a post-approval study is recommended to evaluate the post-market safety and effectiveness of multiple Restylane treatments for lip augmentation. If so, please comment on the safety and effectiveness endpoints that should be assessed, such as adverse events that occur in less than 5% of the population, like necrosis, the inclusion of specific patient populations, such as persons with Fitzpatrick Skin Types IV through VI, younger patients, which we consider to be persons under the age of 40, and males, the duration of follow-up, such as a period greater than one year, to capture multiple treatments, and the study design.

Thank you.

DR. GALANDIUK: I'd like to thank the FDA speakers for their presentations.

Does anyone on the Panel have questions for the FDA? And again remember, we have opportunity for the Panel to address the FDA for questions during the Panel deliberations this afternoon.

Dr. Newburger.

DR. NEWBURGER: Perhaps this question should be directed both to FDA and to the Sponsor. Maybe I missed it in the packet or with the disks, but the MLFS, exactly what were the determining points?

We saw photographs. I assumed that this was agreed upon after extensive discussion with FDA. But how did you actually decide what is

a very thin lip, what is a thin lip? Or is there a ratio? I think that that would give me a lot more help. So FDA could answer.

DR. GALANDIUK: FDA right now has the floor. The Sponsor will have the opportunity to answer that this afternoon.

DR. DURFOR: Thank you very much for that question. This is a very challenging area, as you know. We have heard from the Panel over the last eight years the challenge of trying to develop good scales, and I would suggest that, at this particular time, the company has worked pretty hard at developing a photographic system, and that's what we based it upon, in terms of the descriptors that were provided and the photos that were provided, and the photos that were provided with regards to an attempt to capture a variance of age, gender, and ethnicity. Other thought processes that went into that I will leave it for the company to comment on later.

DR. NEWBURGER: Thank you.

DR. GALANDIUK: Dr. Leitch.

DR. LEITCH: I think it's in the FDA materials that we received regarding -- I think it's Study 13, that there was a death which was -- I think that they're saying it's not related, but it seemed to be related to thyroiditis or thyroiditis is discussed at some point and then thyroid neoplasm. It's sort of an odd death description, and I was wondering if there's any more detail on that.

DR. ALEXANDER: As I understand it, this is a patient who was

found to have a thyroid cancer that was not evident when the patient was enrolled in the study but became evident after she was treated and she died at, I believe, day 28 after treatment, but it was not related to the Restylane at all.

DR. LEITCH: I mean, it's described as a cardiac arrest. I mean, did she have swelling?

DR. ALEXANDER: I don't know the specifics of her death. I just know that it was -- she had metastatic thyroid cancer.

DR. GALANDIUK: Dr. Mount.

DR. MOUNT: I have a question for the statistician. If you use the methodology and the results, how many patients of a Fitzpatrick IV to VI category, extrapolated, would you need to achieve statistical power? Like for an optimal look at this underrepresented population in the study, what would the approximate number be that you would need to see adverse effects in this group?

MR. VAN ORDEN: The power to see adverse effects. Are there specific adverse events that you're concerned about?

DR. MOUNT: Pigmentation issues, granuloma formation, keloid, all those reported, that there were very few of those that happened, but also the number that were enrolled in the study were very small. Would you need 200 or do you need 2,000? I mean, what would be the optimal number for that statistical analysis?

MR. VAN ORDEN: I guess all I can say is, since we didn't see any, we'd be making assumptions about what that rate is. If you want to make an assumption about what that rate is, then we could then calculate the number of subjects that you would need to see. But because without making some sort of assumption about what that is, I can't give you number of how many patients we would need to see.

DR. DURFOR: If I could follow up, we are asking you to comment on a previous study, which was not part of this package. But in that previous study were 150 patients. Fitzpatrick IV, V, and VI were studied and were for injection in nasolabial folds. The incidence of pigmentation changes was six to 9% of the subjects that had those.

So I think the real answer may be maybe we can sit down and calculate that and give it to you in a little bit, if that's acceptable.

I apologize. Charles Durfor.

DR. GALANDIUK: Dr. Newburger.

DR. NEWBURGER: I also have a comment, which is, although there was no pigmentary change reported in this, the subject 08-001, who has Type V skin -- and that's in the FDA handout here -- the lady who withdrew after four weeks because of pain, there is post-inflammatory hyperpigmentation at the right upper lip, at the vermilion. Obviously we don't know the persistence of it, but there is that in this study.

DR. GALANDIUK: And I have a question for Dr. Alexander. You

presented the data about the herpetic outbreaks in the treated patients. It's hard to tell, without getting a denominator of patients who had a previous history of herpetic infections, if that's significant or not. Was it information available to you?

DR. ALEXANDER: I do not know the history of those patients, other than the one who did receive prophylactic treatment. The incidence that we've seen in the adverse events that have been reported elsewhere, in other sites, are comparable. And when you divide the herpes outbreaks into the treatment and no-treatment group, they are also comparable. However, the no-treatment group did get the herpetic outbreaks after their treatment. I do not know the denominators of history.

DR. GALANDIUK: Yes, I think that was an exclusion in the studies, that they couldn't have had an infection for four months previous to enrollment and also couldn't have had several more flares in the previous years.

DR. ALEXANDER: And certainly an active -- that was an exclusion. If they had an active infection of any kind, including herpes, they couldn't be injected.

DR. GALANDIUK: Okay, thank you.

Dr. McGrath.

DR. McGRATH: Yeah, for Mr. Van Orden. You mentioned -- raised several questions about volume. But when you were making your

presentation, you were commenting that some of the swelling and bruising and so forth is associated with larger volumes, but you didn't sort out whether they were given in one bolus or whether that was -- I believe you were adding both the initial treatment and the touch-up. And I would think there'd be a big difference there with regard to the presentation of effects, depending on whether the volume is delivered at one time or over two different injections.

So can you clarify that, if you're going to ask us to talk about total volume as something that you want us to comment on?

MR. VAN ORDEN: I did present it with both the first injection and the total volume, and perhaps it was more clear. The graphs in Dr. Alexander's presentation separate the initial injection from the touch-up injection, and you can look at those graphs to show that it clearly separates that it comes from the first initial injection is where we see the volume and adverse event relationship.

DR. GALANDIUK: I think one of the most notable slides was the less than three and greater than three slide. Is that what you were referring to, Dr. McGrath?

DR. McGRATH: Well, what I'm trying to get at is there seems to be a decreasing trend with each treatment, of the symptoms occurring, in other words, the touch-ups don't have as much and the 24-week ones also have fewer adverse events associated with them than the initial ones, and I'm

trying to get my arms around why you're linking that to volume or whether it's -- you know, what specifically is going on here?

MR. VAN ORDEN: Well, we did see -- I mean, the touch-ups have a smaller volume, and the second treatments had a smaller volume as well, so we see fewer adverse events that may be because of that smaller volume. But as far as -- I'm going to bring up the graph here in just a second -- it is the initial injection volume that we're concerned about.

DR. McGRATH: While you're pulling that up, I had a second question for you. On your slides about the volume injected and the effectiveness, you kept saying that it sort of doesn't correlate. But isn't it possible that to move from one point to another on that scale requires more or less volume, depending on the patient? I mean, it wouldn't necessarily be a direct correlation.

MR. VAN ORDEN: That is certainly possible and that was -- within a patient, volume could make a difference as far as effectiveness, and this study just wasn't designed to show that. We certainly like to believe that's the case, but as far as we know, there's no evidence to know that's for sure the case, that more volume will lead to greater effectiveness even within the same patient, because we only have the one injection, so we can't compare if we had decreased or the change in the effectiveness, if we had increased or decreased that volume by a little bit.

DR. GALANDIUK: Ms. Mattivi.

MR. VAN ORDEN: Does that make sense?

DR. McGRATH: Your endpoint is somewhat objective because it's the judgment of the patient and the person doing the injection, about what's the endpoint, that you've reached the optimal appearance of the lip.

MR. VAN ORDEN: Right.

DR. McGRATH: And given that's the endpoint, you're right, there's going to be a certain amount of variability, so these graphs are going to jump around a little bit to get there. So it's not going to be like a dose response curve for, you know, a medication in the bloodstream. I think you're going to have certain variables here. I'm just trying to figure out how you tried to figure those into your comments because it didn't seem like you allowed for that.

MR. VAN ORDEN: You would expect some variability. I guess we did not expect as much variability. We expected to still be able to see a trend. But as you pointed out on that graph, there are some patients that had a very small volume that saw huge increases and some that, you know, were injected with very large volumes that saw no increase by the longer time point. So I think you're making good comments and good points. I just don't have all the answers.

But in respect to your previous question about adverse events, this one is just the initial treatment injection, the adverse events, whereas this second graph shows the touch-up injections. So the greater concern was

with the larger amounts of moderate and severe adverse events with the initial injection volume.

Does that answer your initial -- the question about safety?

DR. McGRATH: Yes, within the parameters of the events that you're looking at --

MR. VAN ORDEN: Okay.

DR. McGRATH: -- which are bruising, swelling, discoloration.

MS. MATTIVI: And because it was kind of following along the same lines, because the endpoints were rather subjective, did you look at all at the relationship between the volumes and the GAIS scale?

MR. VAN ORDEN: The GAIS doesn't provide for very informative comparisons because everyone was happy. So you can't distinguish between, I mean, any volume at all, and they were happy.

DR. GALANDIUK: Dr. Miller.

DR. MILLER: Yes, if I could just comment on this last discussion. It doesn't surprise me at all that there's little correlation between the volume and the outcome because what matters is the percent increase in volume that you achieve in a lip to move you from one scale to the next.

If you have a very tiny lip and a very tiny volume of injection, and it's going to double the size of the lip, you'll have a significant increase in outcome. If you have an enormous person and you inject a large amount but it only represents 5% of their lip volume, then they're not going to -- you're

not going to see an increase.

So what we don't know in the data is what the starting lip volume is and what percent of that volume does the injection represent.

MR. VAN ORDEN: Again, I'm just a statistician, not a clinician, but I would --

(Laughter.)

MR. VAN ORDEN: -- just wonder, are there are anatomical features that we could measure and should be measuring to -- that would account for this? Because none of the features that we have been able to measure account for this. The baseline lip fullness and other variables have not. So that is part of our question.

DR. ALEXANDER: Janette Alexander.

I must say I totally agree with you. And we were somewhat surprised that there was not some sort of correlation, which is why we began to look at it more. But the study did not take into account anatomical variation, which apparently can be more significant than we thought, and we didn't think of that up front in helping to create the study.

DR. MILLER: If I could ask one more question, I'm sorry. Help me understand what kind of a context to put the adverse event reporting in because there were 120, you know, reported adverse events and we went through all of those.

Now, I would be concerned about that if there were 130

episodes of injection in the world, but there are hundreds of thousands of injections going on in the world of this and we have 120 adverse event reports. So if you could just help me put into context what you presented here, that would be great.

MS. MIRSAIDI: Well, that's one of the problems we have. Unfortunately, not everybody reports adverse events. Not all the manufacturers report every single adverse event. And this is a surprise to us, too; 2003 to 2011 we have only 119 reports. What we can do, we can just look at the proportions or the rate of occurrence in this 120 patients.

DR. MILLER: But within your, you know, FDA world, how do you interpret this type of finding that you have here? I mean, what do you conclude about that?

MS. MIRSAIDI: MDRs are considered as passive surveillance and a signal, just a signal detector. So when we see an increased number of reports saying the same thing over and over, it kind of raises the flag to more investigate and see what's happening. Other than that, MDRs have, as I mentioned, a lot of limitations that doesn't let us come to a certain conclusion or make any rate or anything because we don't have the denominator data either.

You wanted to say something?

DR. DURFOR: Charles Durfor.

I just want to echo the comment, which is one of the great

challenges of MDR reporting, is we'll never know the denominator. But I think we have to keep in perspective why it was important to present the information without giving you a denominator, and that is that as you move forward you want to be aware of all potential outcomes that occur. Many of them, we're not even sure it was the lip that was the cause. I mean, that's one of the problems, 22 versus -- 22 of the reports were reports where you injecting both lips and other parts of the face.

So this is a situation. And we never know how many of these events occur that we never get reports for. It is a voluntary system. So one of the strengths, perhaps, of this presentation is a plea to have better reporting. But the other strength of this presentation is to make sure that you know everything we know in terms of how this product may perform.

DR. MILLER: Thank you.

DR. LEITCH: I just want to clarify. On these graphs that you were just showing us about the volume relationship to side effects, this is two lips combined, right? It's not per lip?

DR. ALEXANDER: That is correct.

DR. LEITCH: Okay.

DR. ALEXANDER: Janette Alexander.

This is two lips combined for the first injection only, this graph. The second graph is both lips combined for the touch-up two weeks later.

DR. LEITCH: Okay.

DR. GALANDIUK: And the graph that was shown with the less than three and greater than three --

DR. ALEXANDER: That was also both lips.

DR. GALANDIUK: -- that was also both lips?

DR. ALEXANDER: Upper and lower. We got that number because of the recommended 1.5 per lip, so three total. That's why it was broken down into those two groups.

DR. GALANDIUK: Mr. Halpin.

MR. HALPIN: Just to add some industry commentary to Dr. Miller's question, if you look at HA dermal filler commercialization in the U.S., first, HA dermal fillers were commercially approved and available in 2003, and then, from the Sponsor's presentation in 2010, there were approximately 1.2 million HA procedures.

So if you think of that time period, there are probably seven million HA dermal filler procedures that have occurred in that time frame, of which a subset, and probably a significant subset, would be Restylane.

DR. GALANDIUK: Yes, Dr. Halabi.

DR. HALABI: Yes. I would like some clarification on Slide 32. So if a patient had a mild and a moderate AE, do you take the maximum or do you count them twice? So in other words, in Table -- on Slide 32, you have 23% mild and less than 1% moderate. So let's say a patient experienced both mild and moderate. Do you count that as two separate events, or do you

take the maximum AE?

DR. ALEXANDER: I believe each patient was counted once. I'll defer to the Sponsor for further clarification. But you're talking about two separate injections, how would they be counted?

DR. HALABI: Over the course of the study. So a patient may have experienced a mild firmness at the first injection, but maybe --

DR. ALEXANDER: Right, but it has -- right.

DR. HALABI: Right, exactly. So I wanted to know how you dealt with that analysis.

DR. ALEXANDER: I'll have to verify that and --

DR. HALABI: Okay.

DR. ALEXANDER: -- confirm that later.

DR. HALABI: Because that may address some of your concern that you raised earlier, if you're taking the maximum or counting it only once. Thank you.

DR. GALANDIUK: Since we have a few minutes, would the Sponsor like to answer that question and perhaps also answer Dr. Newburger's question about the MLFS?

MS. LIN: Xiaoming Lin from Medicis, and I will try to answer several questions one by one. And if I forget some of the questions, please remind me.

And first off is volume versus efficacy there. After we received

the FDA's comments, we did several, several analyses, and we did it by the category, by continuous analysis there and we did a scatter plot. We could not see any relationship between the volume injected and the efficacy results there.

I think there are several reasons for that. One precise reason -- and we talked to all the PIs -- well, not all the PIs, a lot of the PIs -- and asked their insights for that. One thing they told us is exactly what you said here, is the lips have different shapes, different width, different thickness there, and it depends on the width and the thickness of the lips, and different lips require different volumes to achieve a one-grade improvement. So this is one thing.

The second thing is that we have a very, very high percentage of treatment success. So why you have so low treatment failures there, it's very hard to do the correlation there.

The third thing is the patients and the physicians decided to treat to the optimal correction. So we don't have the data to show what's the minimum requirement for the volume to achieve a one-grade success there. So that is the -- because of this reason that we do not see the correlation between the volume and treatment success, and I think it is reasonably so, due to the reasons that I just provided. So this is one thing.

The second thing is that you asked, you know, what's the percentage of the subjects that had the five mL's volume of injection? We did

the search there. The maximum per lip per visit is 2.5 mL's. So we do have five patients who received five mL injections, but those are both lips, including initial treatment and touch-ups. We have three patients who received more than five mL's injection. Those are both lips, including baseline treatment and two-week touch-ups there.

So there was another question regarding what's the percentage of the subjects that had a GAIS improvement at week 24 received the retreatment, and what's the percentage of the subjects that did not have GAIS improvement received the treatment there? So here are the numbers.

First of all, we have 86 subjects with improved or better results per patient's GAIS at week 24, and 80% of them received a retreatment. We have 24 subjects who did not have a GAIS improvement at week 24, and again, 80% of them received the treatment.

The number superficially does not make any sense, but I think it does make sense there. GAIS shows that the subject is happy or satisfied with the treatment results or not, right? And whether they received the retreatment or not, depending on whether they think the improvement is optimal correction, even though they see the improvement and they think they have not maintained the optimal corrections, they still can receive the treatment. I think that's the main reason why 80% of the patients that have improvement of GAIS receive the retreatment at week 24 there.

Another number you asked is that, you know, at week 2, what's

the percentage of the GAIS responders who received the retreatment and what's the percentage of the non-GAIS responders who received the retreatment? And the number is 62% and 72%.

And, again, I think these two things have a little different criteria, whether I see improvement or do I think the improvement is optimal there? So that's why maybe we do not see the correlation for the GAIS treatment success and failure and the percentage of retreatment or percentage of the touch-up there. So this is one thing.

Another thing I want to mention here, talking about volume and AEs. And, again, Medicis did several, several analyses for the FDA, tried to explore that. We do believe this is very important information to provide physicians to guide the physicians and the treatment down the road there.

We did analysis using the continuous model and to assess the relationship between the volume used and AE rate. Specifically more severe ones like moderate AEs, we did not see any correlation there or we did not see the significant predictors for the volume and AE, while we used the category-wise analysis, like FDA showed right there, and we did see that and we presented the data to FDA. And the data shows at initial treatment and it looks like there is a separation at three mL's less or three mL's more, and we think that's important information, and we did provide it to the FDA.

For the touch-up part, there is very, very few severe or even moderate AEs. We did not see the correlation there. And for the

combination, we see some trending there, but the signal is not that strong.

Does that help? Thank you.

DR. GALANDIUK: Dr. Burke.

DR. BURKE: I just wanted to make one comment about the volume and the efficacy.

MS. LIN: Yes.

DR. BURKE: I think implants are very technique-determined and --

MS. LIN: Yes.

DR. BURKE: -- a bigger volume in a deeper layer of the skin has less effect than a smaller volume superficially. And I think that could be one determinant. And that's so subjective because it's difficult for the 12 investigators to have exactly the same technique, and the technique also varies sometimes with the patient, with one investigator and different patients with the skin types. So I think this is a very important variable, and it's close to impossible to be able to study that quantitatively.

MS. LIN: Totally agree. And thank you so much.

DR. GALANDIUK: Okay, we're now going to break for lunch. I would like to ask the Panel members not to discuss the meeting topic among yourselves or with any members of the audience.

We will reconvene in this room an hour from now, at one o'clock. Please take any personal belongings you want with you at this time

because the room will be secured by FDA personnel during the lunch break.

You will not be allowed back into the room until we reconvene.

Thank you.

(Whereupon, at 12:00 p.m. a lunch recess was taken.)

AFTERNOON SESSION

(1:05 p.m.)

DR. GALANDIUK: It's now 1:05, and I'd like to resume this Panel meeting.

We will now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel, present data, information, or views relevant to the meeting agenda.

Ms. McCabe-Janicki will now read the Open Public Hearing disclosure process statement.

MS. McCABE-JANICKI: Both the Food and Drug Administration (FDA) and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

I will go over the Open Public Hearing speaking process to ensure a smooth transition from one speaker to the next.

You will have five minutes for your remarks. When you begin to speak, the green light will appear. A yellow light will appear when you have one minute remaining. At the end of five minutes, a red light will appear and your microphone will be switched off.

The Panel will be given an opportunity to ask questions of the public presenters at the conclusion of the Open Public Hearing. If recognized by the Chair, please approach the podium to answer questions.

I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

DR. GALANDIUK: The first speaker will be Dr. Susan Pope Helman. Dr. Helman, please come forward to the microphone. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting. Is Dr. Helman here?

(No response.)

DR. GALANDIUK: If not, we'll go to the next registered speaker, Dr. Gloria Duda.

DR. DUDA: Thank you for this opportunity to speak today. My

name is Gloria Duda, and I am a board-certified plastic surgeon, and I'm representing the American Society for Aesthetic Plastic Surgeons for the application of hyaluronic acid for lip augmentation. And I have nothing to disclose.

I've been in private practice for 19 years and have been performing nonsurgical wrinkle treatment for all this time and have used hyaluronic acid injectables since its approval in 2003.

The trend for facial rejuvenation is restoration of facial volume, and surgery does not address the perioral aging changes that occur, such as volume loss leading to the long upper lip, the thin vermilion, and the vertical lip lines or the lipstick lines. Correction requires the additional volume with injectables. We are already injecting FDA-approved products, like Restylane, into the nasolabial folds and the marionette lines, and this has been very successful, with great patient satisfaction.

In the United States we have a number of soft tissue fillers available, such as collagen, hyaluronic acid, polymethyl methacrylate, calcium hydroxyapatite, polylactic acid, and fat.

Compared to these other products, hyaluronic acid is the best product for lip augmentation, to correct volume loss in the vertical lip lines. It produces a natural appearance with minimal risks, minimal recovery, good duration of results, it's easily reproducible, and we have high patient satisfaction.

Hyaluronic acid has been approved by the FDA to treat mild to moderate facial creases. It has been demonstrated by multiple authors and literature to be safe and effective in these areas as well as the off-label use for lip augmentation.

There is and has been a high patient demand for treatment of nasolabial folds and marionette lines and lip augmentation in the private practice. I've been using hyaluronic acid since the FDA approval of Restylane in 2003, and we have a high rate of patient retention, with return every 10 to 12 months for additional injections into the perioral area and for lip augmentation.

There are risks with any procedure. However, with the hyaluronic acid they are minimal. Immediately after treatment, there may be mild to moderate swelling and bruising, nodules may form, they're usually palpable but not usually visible, and the product may migrate, but this is not common.

Lip augmentation is a very frequently requested procedure from the younger patient in the 20- to 40-year range for fuller lips, to the 40 to 70-year-old patients to reduce signs of aging, and the results are immediate and reproducible. It's become a very important procedure in our practices.

When we think of lip augmentation, we may think of celebrities like Julia Roberts or Angelina Jolie, and we can achieve these similar results

with hyaluronic acid, if this is the desired expectation for the patient. In my practice, most of my patients are improvement and restoration of just a youthful and more natural appearance, which is easily achieved with hyaluronic acid.

In the recently published American Society for Aesthetic Plastic Surgery 2010 statistics, nonsurgical procedures made up 83% of the total number of procedures performed. Hyaluronic acid injectables were second to Botox in the top five nonsurgical procedures performed, with over 1.3 million procedures performed using hyaluronic acid.

In my private practice, about one-third of my practice consists of one-third reconstructive surgery, and after completion of reconstruction, many of the patients wanted to start to do something for themselves, and a lot of times this includes use of injectables. Two-thirds of my practice is cosmetic surgery, and one-third includes nonsurgical options, with hyaluronic acid maintaining about 40% of my injectables.

I perform over 120 lip augmentations per year with no complications, and the patient is informed that this is an off-label use for the product, and we have 95% retention, with return visits at 8 to 12 months for repeat procedures.

Lip augmentation is a procedure that's already high in demand, and with the FDA approval for this indication, the procedure may become more available to other patients because the application has the FDA

approval stamp. This is very important for patients and for other physicians.

Safety and effectiveness are directly related to the injector's understanding of the product, and the technique and appropriate training for injection techniques may become more available with the approval for this indication for lip augmentation.

Lip augmentation with hyaluronic acid is safe and effective, if it's properly performed, to meet patient expectations with high satisfaction rates. It's already frequently asked for, and it's an important procedure in our practices.

And, again, I thank you for the opportunity to present to you today.

DR. GALANDIUK: Our next speaker will be Dr. Elizabeth Tanzi.

DR. TANZI: Good afternoon. And I'd like to thank the Panel for giving me the opportunity to speak with you this afternoon. My name is Dr. Elizabeth Tanzi, and I am here as a representative of the American Society of Dermatologic Surgery Association. I am a board-certified dermatologist who practices in Washington, D.C., and I have no conflict of interest to disclose for either this hyaluronic acid or any other.

Again, I'm here as a representative for the American Society of Dermatologic Surgery Association. We are 5400 members strong. We're made up of board-certified dermatologists, with a particular expertise in skin cancer surgery, cosmetic dermatology or dermatologic laser surgery, and as

such, at least 75% of our membership are performing dermal fillers, as seen in a survey that was taken in 2009. We are also publishers of the *Scientific Journal of Dermatologic Surgery*.

And my comments will be brief and simple. Speaking on behalf of the ASDS, we find that hyaluronic acid fillers truly were a breakthrough in augmentation when they were first introduced back in 2003. There's no allergy testing required, they're quite versatile, longer duration of action than collagen, and as compared to collagen, we typically use lower quantities for dermal filling defects.

And the perioral area, the lip augmentation and the paramentum area is a popular area. Although it is off label at this point, it is certainly a popular area that has been filled, and we've been using it as such for many years.

In general, as you've been hearing this morning, complications are relatively rare, and we feel they're associated with a poor injection technique typically, such as improper or superficial placement and also large volume augmentation.

And as my plastic surgery colleague just discussed, our classic patients are not those that are looking for giant lip augmentation. They're looking for some return to a youthful lip. And that type of augmentation requires a much smaller volume of augmentation than does, say, the patient who is looking for a specific type of lip, say, an Angelina Jolie type of

augmentation. So the vast majority of patients are asking for smaller volumes. Sensitivity is rare and infection is highly uncommon.

It is our feeling, because the side effects, the more devastating side effects can be associated with improper injection technique, we certainly agree that physicians performing these procedures should have a true appreciation of normal facial anatomy as well as the changes that occur with aging, familiarity with indications, technique, postoperative care, and how to take care of those potential complications should they occur.

And we feel it's appropriate and desirable for those subspecialties, who have an intimate understanding of facial anatomy, to be the majority of the physicians performing these procedures, such as those residents in training in dermatology, plastic surgery, otolaryngology, as well as ophthalmology.

Certainly that doesn't mean to suggest we wouldn't recommend other cosmetically minded physicians from performing these injections. However, it would be suggested that they have additional training and a true understanding of facial anatomy. Because although I wasn't present this morning, I'm assuming that you may have seen side effects related to vascular compromise related to some of these injections, and perhaps if the injector had more of an intimate understanding of the anatomy, I do believe that a majority of these complications could be avoided.

Thank you again for this opportunity to speak.

DR. GALANDIUK: Thank you. In the interim, has Dr. Helman arrived?

(No response.)

DR. GALANDIUK: No. If not, is there anyone else who would like to speak at this time?

(No response.)

DR. GALANDIUK: No, okay. Does anyone on the Panel have any questions for any of the speakers?

(No response.)

DR. GALANDIUK: No, okay. The Open Public Hearing session of the Panel meeting is now closed, and we'll proceed with today's agenda. We will now begin with the Panel deliberations.

Although this portion of the meeting is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that the persons who are asked to speak identify themselves each time. This helps the transcriptionist to identify the speakers.

Is the Sponsor prepared to respond to the Panel's questions posed this morning? Does any Panel member have a question or a comment for the Sponsor or for FDA?

DR. LAWRENCE: Yes, please, Dr. Burke.

DR. BURKE: Yes, I just have one question to the Sponsor. Could you tell us about the number of patients that have been seen with kind of vascular necrosis or necrosis problems in injecting the nasomelial area? In other words, I just wanted to have -- with the large population that you've been following since 2003.

DR. LAWRENCE: I don't have specific numbers, but I can speak in general terms, if that's acceptable, Dr. Burke, because I review all of the pharmacovigilance data. This is Ira Lawrence from Medicis. I apologize.

We review adverse events on an annual basis for trending. The incidence of necrosis associated with the use of dermal fillers is exceedingly rare, certainly less than one event per year that we have seen in general. There have certainly been cases reported. Often it is due to the incorrect placement of the filler in areas such as those around the glabella or areas where there is much more vascularity than the nasolabial folds. And also the depth of injection also has a significant impact.

But we have seen cases. I just unfortunately can't give you a direct number, but it is exceedingly infrequent, but certainly has been reported. And we have not seen any cases, obviously, in our clinical study, although I point out that these were experienced injectors as well.

Does that answer your question? I hope. Thank you.

DR. GALANDIUK: Dr. McGrath.

DR. McGRATH: While you're at the microphone, one of the

questions that the FDA raised was -- it had to do with youthful patients and the possibility that they would be treated repeated times. I was wondering if you had any data from your past experience with the product in patients where it's been used repeated times in another part of the face, because that might help us to understand what happens over time, if you know of situations where patients have had multiple treatments over years.

DR. LAWRENCE: Actually, I would actually like to ask one of our clinicians, Dr. Robert Weiss, who has an extensive experience utilizing this, to comment. He does have a number of patients with repeat exposure.

Dr. Weiss.

DR. WEISS: Yeah, I've been following a number of patients now, and I can't give you the exact number, but since 2003, 2004, and it's 2011, and what I find is that they require, just like in this study on the repeat treatment, less volume each time. And so the incidence of side effects and complications actually is reduced over time. That really sums up my experience.

DR. McGRATH: One question, I think, that had arisen was whether there was more difficulty injecting the material when you went back at 24 months. So from your experience in other parts of the face, is it more difficult to implant the material when you do it the third, fourth, fifth, sixth time over a long period of time?

DR. WEISS: Yeah, I've actually found the opposite, that it

actually becomes easier. The tissue, subcutaneous tissue or dermis, just seems to be softer over time, and you're not having to expand the volume as much as you do the first time because the first time you may be using one to two cc's. I'm talking about the nasolabial folds now. And then when you go back, it's kind of already expanded and it's very easy to maintain that same level of correction.

DR. GALANDIUK: We'll first have Dr. Mount and then Dr. Newburger.

DR. LAWRENCE: If I can also add that -- also my staff reminds me of the things I forget as I get older. We actually have followed patients in a study for up to periods of 36 months, with at least six retreatments, and in those cases we've seen no difference in the adverse event profile. In fact, as we've discussed earlier, in fact, sometimes the frequency may go down. I think our conclusion would be that there's really no difference over time with regard to adverse event profile. I'm sorry.

DR. MOUNT: Thank you. Is there any difference in the time of effect or the resorption when it's placed in the lip in a submucosal versus a subdermal plane? Have you noticed that or any of your clinicians noticed any difference in time to resorption?

DR. WEISS: Sorry. What was the duration --

DR. MOUNT: The duration of the effect. Is it different --

DR. WEISS: Oh, for submucosal versus intradermal.

DR. MOUNT: Subdermal.

DR. WEISS: Subdermal. I think it's more of a function of movement and dynamic remodeling. So if you put it in areas, for example, another off-label indication, if you put it up here in the cheeks to sort of give the face a little bit of lift, that seems to have much longer duration than areas with more movement.

DR. FEW: I definitely agree with that. And really the issue is either submucosal or intramuscular because, typically, as you're injecting deeper, I think it's fair to say that probably in many cases you're planting it right along the orbicularis oris, and as you get it closer to the muscle, the longevity seems to go down.

So it's kind of finding that, really, if you will, that sweet spot between the two layers. But in general, you want to get it as deep as you can, in my opinion, without getting it into the muscle to kind of find an optimal effect.

DR. GALANDIUK: Dr. Newburger.

DR. NEWBURGER: Amy Newburger. I have two questions.

Number one -- well, let me say the questions first and then you can order whichever. I'd like, if you could, to give more detail about how you precisely developed your scoring system.

And number two, did you notice a difference in the adverse event profile and in the longevity between those who were stratified

according to wanting to change the shape of their lips versus those who were looking more for rejuvenation? In other words, I would think that the profile of the younger individuals were going more toward a fashion issue and those who were older tend to want to restore what had been a youthful volume. Did you see any difference in side effects?

DR. LAWRENCE: I'm going to ask Ms. Lin to address those questions, I think, starting with your first question about the development of the scale. And I am not sure, to be honest, and we'll look into it, whether we collected specifically the reason why the patient was seeking augmentation. But she may be able to answer that. So Ms. Lin.

MS. LIN: My name is Xiaoming Lin, and I'm from Medicis.

That is a wonderful question, how we developed the Medicis Lip Fullness Scale. And I want to start with really the first pilot study, the 13K. We did not talk about the details of the study. Actually, in that study we have three camera systems, two 2-D systems and one 3-D system. We measured 20-some parameters of the lips there to see what's the difference there, what's the change, and try to find the clinical meaningfulness of the measurement.

So after the study was done, we had a meeting, advisory meeting, with about 10 physicians and go through the data and seek input. What is really the clinical meaningful change for the lips there? Out of the meeting -- and most of the physicians told us that lip fullness is really the

meaningful change and that that is what a majority of the people are looking for there. And also, in the treatment there, you can also define the vermilion border as well. So from that meeting, we take it that the working task is to develop a lip fullness scale.

So then the question is how you divided the lips to five scales, right? We worked with five physicians. We took over 200 photos using the standard camera, of a Canfield camera there. The amount over the 200 subjects we took photos, we had at least 50 of them are males, at least 50 of them are females, and at least 50 of them are younger, and at least 50 of them are older, and at least 35% of them are Fitzpatrick darker skin types, or we call that minorities. We do that in order to capture the full range of the lip fullness and in order to look at them and then develop the scale there.

After taking all of those photos there, we sent the big binders of the photos to physicians, five physicians. We asked them to put the lip scales into the grades, and we do not give them any directions as to how to do that. So we want to see how they do that, right?

And after giving them several weeks to work on that, we called four physicians and had a four-day meeting with them. The meeting was at Canfield there. We reviewed how they divided the lips into four scales or five scales, and how they did that.

For example, Dr. Michael King is one of the members that we worked with. At the very beginning he put the lips into five buckets there.

It's one-fifth, the lowest end is very thin lips there, and one-fifth of the other end is very full lips there. And the other physicians we worked with, and thinking that this is how they would divide the lips in different shapes and fullness there, because that is clinically meaningful, we reviewed with them one on one and why they chose that. We also took all the scores of five physicians and put it in the spreadsheet there and then bring the pictures to the projector and review with the whole team and to say, why do you do this, why you put it in there?

And at the end, we come to the consensus that we divide it into five scales there. We do the five instead of four because four scales is much easier to validate, the difference is much easier to differentiate there. But potentially we are afraid we could over-treat the patients by bringing the one grade to another there.

So after the whole-day discussion there, we decide that we have a five-step scale there, and we put the photos on the wall there and tried to satisfy the different angles, why we divided the photos in that way.

Does that help?

DR. NEWBURGER: That helps, but it's basically then subjective. There's no particular ratio or there's no degree of measurable change in -- if you had the Canfield 3-D, there wasn't something where you could find the area under the curve between -- I'm just wondering. Is this, well --

MS. LIN: I agree.

DR. NEWBURGER: -- a best match for this type? Because that then explains to me a great deal of the variation between observers.

MS. LIN: I think yes and no, and I think of the no part, no, that we do not have a specific measurement saying it's one to two millimeters or one to two centimeters -- this represented grade one or grade two -- because we have a very difficult time to cut off, and we have a very difficult time to just justify that 1 centimeter thick, it's one, but 1.1 centimeter is two, and what's the clinical meaningfulness there? But at the same time, there are some measurements in there. I think these five grades, it's almost equally distributed among the lip fullness there.

DR. NEWBURGER: Thank you.

DR. GALANDIUK: Dr. Miller.

DR. MILLER: Yes, thank you. Dr. Lin, I have a question for you.

So it sounds like you had the data from these digital photos, and it would've been possible to do some sort of quantitative analysis based on pixels or something to really look at lip changes. And I mean, I think I agree, you need to have the qualitative subjective assessments because aesthetic surgery basically comes down to that.

MS. LIN: Yes.

DR. MILLER: But if you wanted to demonstrate that you're changing lip volume, it seems like you would've had the data to do that.

MS. LIN: We actually did, and let me tell you why we did not go

with that route there. And this is a wonderful, wonderful question there. And first of all, we did have the 3-D photos there, and it changed the measurement there. So let me tell you a couple of the challenges there.

First of all, if you measure the lip in this area and after the treatment the lip is bigger, it could go out of your measurement area there, and that change of the lip there really does not fully represent the change of volume of the area you measured there. But if you changed the area, you measure the volume before the treatment, and after the treatment to capture the full lip there, but it does not really represent the true volume change in certain areas there. So this is one thing.

And we also looked at, for example, the lip surface area change. We looked at the lip length change, height change, and even looked at the Cupid's bow to the base of the nose. The distance shortens there, and we measured 20-some points there. It is hard to justify. Two people said, if you have changed from this to this, it is a clinically meaningful result. That is why we did not go with those measurements. That is why we go with the MLFS.

DR. MILLER: Okay.

MS. LIN: Thank you.

DR. LAWRENCE: If I could ask Dr. Weiss to comment as well from clinical experience.

DR. WEISS: Because it's a really important question that you've

asked and a really important issue to address, and I think there are several problems that we were confronting at the time. First of all, there were no -- like these days we have the Canfield 3-D vector, which is like in a real usable stage, and probably if one was designing the study today, 2011, that would be probably pretty reproducible, but we'd have to test that as well.

The other problem is that we don't have -- the lips aren't a cylinder like a can of soup. I've used this analogy before. It's more like a croissant, and you've got different areas of different volume and with all the different shapes. So I was also skeptical, and this is like the most difficult part of the study.

But once we spent that time and divided it up into the five categories, you'd be amazed. Like if you study that scale and then you go around to every member of this Panel, you'd be able -- with their lips parted like this, you know, because I can make my lips disappear, going like this, that's the other issue as well. But I could look at Mr. Halpin, for example, and the expression that he has now, he's a one on his upper lip. I mean, it's really --

(Laughter.)

DR. WEISS: So I picked on a male because I knew that would be easier. But I'm just making the point that you'd be amazed. And there was significant amount of time spent in training, as well, during the investigators' meeting. I mean, several hours was spent on this so that it would be

reproducible from site to site.

But it really -- it did work. It seems like at first, well, there's nothing quantitative. It's sort of, you know, analog. It's not digital. But you know, the FDA was consulted on this as well and agreed that this would be a valid scale. And certainly, you know, for each individual grader it's valid.

Some people are harsher graders than others, and there were no specific instructions given. Like if you think it's somewhere in between, to go to the next highest or next lowest, and I think that's where you see the less consistency from investigator to investigator. But within each investigator, I think there was a lot of consistency, and that's how I interpreted that data. But, you know, you bring up a very important issue, but it worked.

DR. MILLER: I still think it would've been useful to have that data because you may not have had a third of untreated patients being graded as responders.

DR. WEISS: Then you get from like the live visual assessment and then translating that to two dimensions again onto the photograph. But I think we overcame these issues in a really good way. Oh. I think we overcame these issues in a really good way. But I'm satisfied and proud of these results.

DR. LAWRENCE: Dr. Few would like to make a comment as well, please.

DR. FEW: I think kind of looking at it -- and once again I'll say the same, I agree that there are inherent limitations to the scale. But at the same time, as you know, as a plastic surgeon there are truly three-dimensional things going on, the cutaneous height of the lip, the vermilion length, height. And certainly that changes with underlying maxillary bone changes, with aging. You have nasal changes.

I mean, the focus of my practice is really on facial aesthetics and this is -- it's a challenge. It's a challenge actually, as you know, on the -- really on really quantifying surgical results as well.

And so I think that really is what the Medicis lip scale more or less does, is attempts to validate a relatively subjective/objective point of analysis in terms of thin, very thin, moderate, and so on, and have a reproducible kind of clinical assessment tool.

So I think I'm not up here to say that it's perfect; I would not say that. At the same time, we played with a lot of different ideas prior to putting the study together and relied heavily on the FDA to develop this tool.

DR. LAWRENCE: Thank you, Dr. Few. Yes.

DR. HALABI: Yes. Did you collect information on the agreement among the evaluators at baseline? Because I haven't seen -- or maybe it was presented then. I did notice that. I haven't seen any slides on agreement among the evaluators at baseline because I think that would be also important to give us a sense.

DR. LAWRENCE: I'll ask Ms. Stacy Woodard, who is our statistician, to comment. Although I do think it's important to note that, at least in the case of the blinded evaluator, they actually did not review the patient at baseline in order to maintain the blind. But Ms. Woodard can speak to that.

DR. WOODARD: This is Stacy Woodard again.

Again, as Dr. Lawrence just said, the blinded evaluator did not assess the patients at baseline or week 4. They didn't see the patients until week 8, so we do not have those assessments to compare. We did not compare specifically the results between the treating investigator and the IPR.

Wait a minute, I take that back. We do have that. Hold on. Let me go look it up, and I'll get back to you. We did look at the results for each agreement between each evaluator over time.

DR. HALABI: When you looked at agreement among evaluators at week 8, did you look at that based on the five categories, or did you look at that as a response versus non-response?

DR. WOODARD: We're actually done it both ways. In the protocol, we're just looking at response, and then based on an FDA request, we did look at it on all five of the categories.

DR. HALABI: And is it possible to look at that slide? Because I don't think I've seen that.

DR. WOODARD: Yeah, let me see if we have a backup slide.

DR. HALABI: Okay.

DR. WOODARD: If not, I'll get you that information.

DR. GALANDIUK: While the Sponsor's checking that, Dr. Mount and then Dr. Leitch.

DR. MOUNT: Thank you. Del Mount. I actually have a multi-tier question.

And I noticed that you were very careful in your study about the age limitations and particularly very careful about pregnancy, very specific about avoiding pregnancy during the study on the lip, and I actually have a couple of questions regarding that.

First off, I would -- and tell me if I'm wrong about this, but I would expect that perhaps a younger woman might be more interested in having lip augmentation than treatment of nasolabial folds, which means that the hyaluronic acid would be implanted at the time that she might still be of childbearing age.

And my question is, first, is hyaluronic acid any sort of teratogen? Does it have any sort of ill effects on a pregnancy? And if it doesn't, why were such careful analyses done on women that were avoiding pregnancy at all costs?

DR. LAWRENCE: I can answer the second -- the question about teratogen. No, it is not a teratogen. Ms. Lin may wish to comment on why

we specifically precluded patients who were pregnant.

MS. LIN: Thank you. My name is Xiaoming.

And this is really not done specifically to exclude a pregnant woman for Restylane. This is a common practical -- it's really a common practice for all clinical trials there. So we really just did not deviate from the common practice of a clinical trial.

DR. MOUNT: Okay. And then, to follow up on that question, are there any recommendations in the package insert or instructions, for example, to avoid giving during pregnancy? Or is that not a contraindication for either nasolabial folds or lip augmentation?

MS. LIN: It says it has not been studied.

DR. MOUNT: Okay, all right. And then my last question. And this is just kind of a silly question, I guess. Why is this a device and not a medication?

(Laughter.)

DR. MOUNT: So why did it come through the devices panel --

DR. LAWRENCE: I will defer to learned colleague Dr. Durfor, who I think may be able to address that more clearly. Thank you, Doctor.

DR. MOUNT: Maybe I should've asked that one first.

DR. DURFOR: Charles Durfor.

Hyaluronic acid in this particular use is believed to be a physical space filler. Because it is a physical space filler and not a chemical space

filler, a chemical reaction, it's classified as a device.

DR. LAWRENCE: Thank you, Dr. Durfor.

DR. GALANDIUK: Dr. Leitch.

DR. LEITCH: I don't think this has been discussed yet, but I'm going to go ahead and bring it up. In looking at the photos that we were supplied, I was sort of disappointed in the appearance. It seemed like a lot of the patients had loss of definition of vermilion border, some hyperpigmentation above the lips. And you know, obviously in the end, if a person thinks that looks okay, then, you know, that is as it is. But I was wondering, you know, is that a problem in how the injections are done or was that the desired effect?

DR. LAWRENCE: I will defer to one of our treating physicians, who actually can comment more on the desired effect of the patients. Perhaps, Dr. Smith, you might to comment.

DR. SMITH: Hi. Stacy Smith.

So your question is, some of the photographs that you saw may not have been maybe what you thought was a great aesthetic outcome, given what the patient looked like. And I'll tell you, in the treatment of patients for aesthetic indications, it's very much an interaction between the patient and the physician about what the desired outcome is and what you can achieve.

Many cases with lips, et cetera, you'll inject a certain amount of material and it's an ongoing process. The subject will look at the appearance

in a mirror and you may inject more. They sometimes may want more than you think is what you would like, but you satisfy them, knowing that the risks are low and that they will enjoy or get the effect that they want. So many times you wind up treating to their subjective desired outcome and not always the same outcome that you may have.

DR. LEITCH: So you don't think those -- I mean, I was wondering, you know, if the instructions for how to do the injection were a little more precise or some way -- I don't know, maybe it just doesn't work that way, but that the filling could be more directed as opposed to blunted. Because some of these lips were kind of clown-looking at the end, and there was loss of -- you know, loss of the normal contour and beyond the vermilion edge.

DR. SMITH: Great. And sometimes there is a very distinct and beautiful and fine outline to the lips, and sometimes there's a more broad enlargement of the lips. It's been my personal experience that many times I try to create that really defined curve to the lips and the patients will say, no, I'd like them bigger. It happens again and again, and you actually wind up injecting more material and going beyond what you personally may think is your favorite aesthetic outcome, but the patient is much more satisfied with that particular type of outcome.

With respect to injection instructions, there was instructions about how to inject the material, where to place the needle, how deep, basic

techniques. With the respective instructions on what to achieve, it was basically the optimal cosmetic outcome as determined by the patient and the injector.

DR. WEISS: Bob Weiss.

I think part of the problem, too, is you're looking at two-dimensional images, and certainly, at the 72-hour point, you're going to see people with more swelling. But there are a number of -- like at the Baltimore site, people, the first thing they say is no, I don't want those huge lips, whereas if it's on, you know, New York or Miami, that's the desired look. And I think the trend now, if you look online, is that it's no longer the huge lips. So that might look weird to you, but I think it's also a problem with the translation from a 3-D perspective to a 2-D image.

And the analogy I use in that case is, typically, when you're watching golf and, you know, you're watching Tiger Woods and he's looking at that and you see how the ball moves and you have no idea. I mean, there can be five feet of elevation, but even on an HD screen, you're not seeing that. And I think you lose a lot by looking at the two-dimensional images, and so it might look strange to you.

And also, you know, as time goes on, when you look at people at the end of the study, it kind of gets incorporated, and it has a much more natural and soft feel, and that's why the demand, I think, continues to go up because I think, initially, there were issues like you were bringing up. But I

think we understand why that happens.

DR. GALANDIUK: Dr. McGrath.

DR. McGRATH: I have two questions. One, when you did this, you tended in about 70% of them to do a touch-up. So is your recommendation for the product going to be, to the user, to do an initial injection and then consider returning in two weeks for a touch-up, with the expectation that that would be useful?

Because I'd just like to hear from the different clinicians who were doing this, because clearly you would find it gave you more control by doing it in two stages than trying to do everything at once, unlike the nasolabial creases, where that's not an issue. Therefore, are you going to make that part of your marketing of this product, and how are you going to handle that?

DR. LAWRENCE: I'll certainly defer to our clinicians, since I don't inject, and luckily for the patients, I do not. Seriously.

However, I think certainly from a promotional standpoint, the promotional activities would be based on the final IFU because we cannot promote except if there is a recommendation for touch-up.

That said, I think we have felt, from the study that we conducted -- and I'll ask our colleagues to comment -- that many patients did benefit from returning. As it was alluded to earlier, there may be some additional swelling and deformity that, as it resolves over that first two weeks

and then patient is reevaluated, you may be able to touch up and obtain an optimal result. But I'll ask Dr. Weiss and Dr. Smith to comment on that.

DR. McGRATH: Just before you leave, I think I understood your second half, but what was that very first beginning part you said about marketing?

DR. LAWRENCE: You were mentioning about promotion.

DR. McGRATH: Yeah.

DR. LAWRENCE: We can only promote to whatever would be in the instructions for use. So if a touch-up is included in the final labeling, if the product should be approved, then we could promote that. Only if that is the case can we promote, however. Just to understand from a compliance standpoint, we can only promote what is actually included in the labeling. So if there is a recommendation for touch-up, then we would certainly be promoting to that. If that is not included, we cannot promote to that.

DR. McGRATH: But at the present time, you haven't put that into the verbiage that you've come up with so far for your suggested ideas about how you want to market it?

DR. LAWRENCE: I think that's something we'd be subject to a negotiation discussion with the Agency, that's correct.

Dr. Weiss.

DR. WEISS: Bob Weiss.

What I personally found in the study is that you couldn't take a

someone with a type one lip and turn them into a type four at one sitting. It's just not possible. But serially -- and this is partially the study, but partially my experience over the years, you can sort of achieve, based on the patient expectations. You know, the slow but steady method is certainly safer. The patient likes it a lot better because there's much less swelling. And what happens when you fill to a certain volume, it actually just goes back into the soft tissue of the upper lip and you're really just wasting product, too.

DR. GALANDIUK: If we could please just have one person from the Sponsor standing at one time and coming to the podium. Thank you.

Dr. Miller. I'm sorry, Dr. McGrath, did you have one part of your question not answered?

DR. SMITH: Stacy Smith.

I just wanted to add some additional comments with respect to what Dr. Weiss was covering. A couple of things.

From a regulatory or a trial design perspective, virtually every dermal filler that's been approved has been approved with a treatment and a touch-up, and that's designed to give the products their optimal chance to show benefit.

That being said, too, these products, it's much better to undershoot than overshoot. It's like blackjack. You don't want to go over because it's hard to fix these problems. So starting with a modest amount and then allowing a touch-up to get to the final result is a much safer process.

DR. McGRATH: I had a second question. Should I do it now or come back to it?

DR. GALANDIUK: Let's do Dr. Miller first. Dr. Miller.

DR. MILLER: Yes, Michael Miller. I have a question for the clinicians, also.

If you can remember back to when you started doing this and if you could comment on what kind of learning curve you encountered and what kind of major mistakes you felt you learned about that, you know, everyone else needs to know about it.

And if you could comment second on the idea that probably a lot of clinicians are going to be doing this, I mean, including dentists and you know, surgeons and non-surgeons and maybe practitioners. I mean, a whole range of people who take care of patients may decide to get into this. So what kind of training would you recommend? If you could comment on that, I'd appreciate it.

DR. LAWRENCE: I'll start with Dr. Weiss, please.

DR. WEISS: Thanks. Robert Weiss.

You know, it took probably several months to feel comfortable. I'm trying to go back to, you know, a number of years ago to do this, and I think the main things that I learned was -- or observed is that I had fewer issues if I injected very slowly, if I didn't overcorrect, if I didn't put in too much volume.

And, you know, we certainly push the companies to mix lidocaine in with that, because one of the problems was, when we first started, we had to do blocks of the area, and what happens is, when you do a block, then the muscle tone changes, so you can't really see the shape of the lip. So I think with that available too, that makes it a lot easier. Those were the main things that I observed.

And I think one of the advantages to have the indication -- because I think the situation exists right now that, you know, many states are passing laws that dentists can do it, and if the companies are restrained and they can't talk about it, then you're going to get people who order the syringes and they're going to do it without the proper training, and it's going to lead to an increased risk of side effects.

And I think the path to proper instructions from experts who've had many years of experience, it is to make it an indication and to expand this indication for the lips, so that proper instruction can be given both by the company and not just in CME events. Thank you.

DR. GALANDIUK: Ms. Brown.

MS. BROWN STRONG: Earlier you described three different methods -- I'm sorry, this is actually related to the injections as well. But you described three different ways of injecting, and I didn't know if there was a recommended way or preferred way or if it's a combination of the three different ways and if that's part of your plans for training, if you go that

direction.

And then, secondly, I know I heard someone say that it was removable, and I was curious if that is by steroid injections or how it is that you do that.

DR. SMITH: All right. So taking the second question first, removability, these are hyaluronic acid products. There's a product that is used off label, hyaluronidase, that actually dissolves the material. And hyaluronic acid fillers are used in a variety of areas, and when there is an error or a misplacement, the material can be rapidly dissolved by the injection of hyaluronidase and can often simply resolve a misplaced product. So that's what I would call removal.

And then, remind me of your first question again.

MS. BROWN STRONG: I think it was you that described the three different techniques of injecting, and I didn't know --

DR. SMITH: Sure.

MS. BROWN STRONG: -- if there was a recommended one that needed to be taught [sic].

DR. GALANDIUK: And, Dr. Smith, if I could ask you just to identify yourself --

DR. SMITH: I'm sorry.

DR. GALANDIUK: -- for the transcriptionist. Thank you.

DR. SMITH: Sorry. Stacy Smith. My mistake.

Yes, the three injection techniques, to review, are retrograde linear threading, where the needle is advanced, the material is injected and withdrawn, very similar to a caulking gun; and then there's antegrade, where the needle is partially advanced and the material is injected and the needle is advanced as the material is injected to sort of have the material flow ahead of the needle point; and the last is simple, what we call serial puncture, where you simply put the needle point where you want to have the material implanted and implant a small amount of material and then move the needle point somewhere else with a new puncture.

Of those three, retrograde linear threading is probably the easiest, the easiest to teach, and likely to be the safest and it's commonly used for vermilion border augmentation.

And when the question was asked by Dr. Miller, I thought back to when I was learning how to do this a long time ago and with other products besides this product. Retrograde linear threading made the process very easy, very simple, and honestly, it is really not terribly different from nasolabial fold implantation.

DR. LAWRENCE: And I think, Dr. Miller, to your point, I think that is one of the reasons, as I mentioned in my closing statements, why we think it is so essential to actually have the indication that does, as Dr. Weiss and Dr. Smith alluded to, allow us the ability to truly train appropriately for individuals that wish to use the product.

And I think also, to the comment that you had, ma'am, I think that would be something -- that certainly the technique was allowed, a variety of techniques were permitted in the study, and I think we would certainly work with the Agency on providing that appropriate information in the package insert.

DR. GALANDIUK: Dr. McGrath.

DR. McGRATH: Some of the exclusion criteria were some medical conditions, and I was thinking about this and thinking that probably you wouldn't -- I would ask the clinicians. They would probably not want to proceed in the face of some of these things.

I was looking at the list that you had. You had psoriasis and herpes. Certainly actinic keratosis to the lower lip, someone who has chronic cheilitis. I would say anyone with any history with angioedema or anything like Melkersson-Rosenthal, I mean, how are you going to keep these -- what provisions are you going to make for patients with these problems? Because these might not show up as the early complications that you're collecting here, but these could be long-term, more severe problems.

DR. LAWRENCE: Well, I think certainly these are excellent points, and I think we work closely with clinicians and with our clinicians at the Agency to identify patients that may be a potential risk for an increased incidence of an unusual adverse event.

We are relatively careful when we do our clinical studies to

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have these exclusion criteria, and that is why we put those in, because those are built in, then subsequently in the IFU, those certainly can be incorporated. I acknowledge we are not exhaustive and sometimes do miss some of these additional concerns, and I think that is something that we will need to pay attention to.

And I think that also comes out of training. I think, as we hire and utilize professionals that have utilized the product, both off label and also in their practice, I think those are people that bring a great deal of experience to the table as we design our training materials, to Dr. Miller's point, and I think that would be something we would certainly include in the training materials as well as any precautionary statements.

DR. McGRATH: I understand. I wonder, though, if it would go beyond a precautionary statement. I mean, would you see anything that's contraindication to it?

DR. LAWRENCE: That I don't know if our colleagues -- one of our colleagues, perhaps, Dr. Few, you would like to comment on any areas where you think it might contraindicated?

DR. FEW: No, I would definitely agree with Dr. McGrath. I think that there are preexisting conditions that would pose a relative contraindication.

Actually angioedema, I definitely have seen patients who have just spontaneous or idiopathic angioedema of the lips. Sometimes they'll

attribute it to certain food dyes or preservatives. That's typically a patient that I will proceed very cautiously with or not treat at all. Obviously, if you have a question of some kind of cancerous lesion, you work that up first. You wouldn't inject that patient. Cheilitis, I agree with that, that's a condition that I would tend to avoid.

So I mean, really it kind of almost falls into buckets of either neoplastic conditions that are undiagnosed, untreated, untreated infectious processes that, again -- and this kind of falls in line, if I'm not mistaken, with even the nasolabial fold indications, where if you have those underlying conditions, it's really -- it's considered a relative contraindication to treatment. So I think you're bringing up a great point.

DR. GALANDIUK: Expanding on Dr. McGrath's questions regarding immunogenicity of this product, in the patients that had severe adverse reactions, was there any history of prior gram-positive infections?

DR. LAWRENCE: That's an excellent question. As you're aware, in the early studies, there was some evidence that patients who had been having previous strep infections do mount antibody responses. Those responses have not been associated either with a loss of efficacy or an increased incidence of adverse events.

We did not specifically look in this study for antibody presence, although we have done it routinely in the past, and actually, of course, of particular of interest of mine as a clinical immunologist, we also frequently

get requests by physicians in our post-marketing surveillance for patients who had a reaction that may be perceived as having an immunologic basis, and we in those cases routinely, at our expense, actually, evaluate those patients for the presence of either Type I or Type IV, so either IgE or IgG cell-mediated immunity. We have not yet to date been able to demonstrate any such activity. This has been done in work done with Dr. George Murphy at Harvard, and Dr. Robert Hamilton at Johns Hopkins.

I'm sorry, I forgot again. This is Dr. Ira Lawrence. I apologize.

DR. GALANDIUK: And also in your materials you recommend that this product not be given in patients who are immunosuppressed. And as you know, there are so many patients right now that are getting all sorts of different drugs, including anti-TNF products for everything from rheumatoid arthritis to psoriasis. What would your labeling be for patients who are on products like that?

DR. LAWRENCE: I think, in general, much of this is based on the original labeling that we negotiated with the Agency for the nasolabial fold.

And I think, again, to speak to Dr. McGrath, I think this is a very conservative approach. We're always concerned about the potential of introduction for a potential infectious agent, especially when you're transposing the cutaneous barrier.

So I think again we tend, as a company, to take a relatively conservative approach to those type of patients. They happen to be patients

I've treated for a lifetime of transplantation. So I take it very seriously.

DR. GALANDIUK: Ms. Mattivi, do you have any questions to the FDA or to the Sponsor?

DR. LAWRENCE: Dr. Galandiuk, there was a question still open from -- we do have the answer to her question, if that would be acceptable for us --

DR. GALANDIUK: Please proceed.

DR. LAWRENCE: -- to bring this Ms. Woodard back up. Thank you.

DR. WOODARD: Hi, again, this is Stacy Woodard.

So to answer the question about the agreement at baseline between the treating investigator and the only other evaluator we have, which is the independent photo reviewer, so it's a potentially biased analysis because to get in the study, the patients had to have very thin or thin lips at baseline, per the treating investigator.

When the independent photo reviewers reviewed the photos, they didn't know which patient and which time point they were reviewing. So the independent photo reviewers could rate the baseline photos from very thin all the way to very full.

When you do the agreement between that, you get that five-by-five, you know, cross-tabulation. There's a bunch of zero cells in there because the treating investigator could only rate as one or two. So I couldn't

calculate a kappa. But if you look at the agreement, the agreement was 25% in the lower lip and 41% in the upper lip.

DR. GALANDIUK: Okay. Mr. Halpin, do you have any questions for the FDA or the Sponsor?

MR. HALPIN: Not at this time.

DR. GALANDIUK: Mrs. Brown? No, okay. Dr. McGrath? Dr. Burke? No. Dr. Mount? Dr. Leitch? No. Dr. Newburger? No. Dr. Miller? Dr. Halabi? No, okay.

DR. LAWRENCE: Okay, thank you very much.

Dr. Galandiuk, I apologize. We did have two updates I completely forgot, from the earlier session this morning, that we wanted to provide since we had committed to those, if that's acceptable.

DR. GALANDIUK: Yes.

DR. LAWRENCE: Again, Dr. Ira Lawrence.

The first was the question, I think, Dr. McGrath, you asked about the patient with thyroid cancer in the 13 study, the -- I'm sorry. That patient was an 80-year-old male who had not previously been diagnosed but in fact was deceased overseas as the result of a cardiac arrest. He was diagnosed with metastatic medullary thyroid carcinoma. He was 80 years old. Unfortunately he did die overseas, so we have no other information other than that.

And then the second question that I think Dr. Newburger asked

or commented on was about the African-American patient and hyperpigmentation, and we have more information that Dr. Few can comment on, please.

DR. FEW: I think that's a very astute pickup, and in that particular patient's case, she actually had post-injection herpetic outbreak, and so then she had post-inflammatory hyperpigmentation in that spot. And I was able to look at the file for that subject, and it's interesting to note that even though she did drop out of the study for unknown reasons, her GAIS scale, her self-reported scale was very, very satisfied. So I think it's certainly an interesting additional bit of information. Thank you.

DR. GALANDIUK: Okay, we're now going to proceed to the FDA questions, and we're going to focus our discussion on the FDA questions. We have a number of complex questions today, so please refer to the copies of the questions that you have in your handouts. I would ask that each Panel member identify him or herself each time he or she speaks to facilitate transcription.

Please show the first question.

DR. DURFOR: The first question:

The incidence and duration of adverse outcomes reported in patient diaries after the first Restylane injection were presented on Tables 17 and 18 of the Executive Summary. Most subjects (99%) reported adverse outcomes, and 41.5% of these patients reported adverse outcomes that

affected daily activity or were disabling. The most common adverse outcomes (i.e., bruising, redness, swelling, pain, tenderness, and itching -- they were the most common adverse outcomes), and most (85%) resolved within two weeks. Fifteen percent of the events (typically swelling and tenderness) lasted longer than two weeks.

The incidence and duration of treating investigator-diagnosed treatment emergent adverse events reported in 5% or greater of the study population are also presented in Tables 14 and 15 of the Executive Summary.

Lip texture, firmness, and symmetry assessments were discussed on page 35 through 39 of the Executive Summary.

The results of the Sponsor and FDA assessments of the Medical Device Reports for use of Restylane off label in lip augmentation are presented on pages 29-30 and 30-35 of the addendum to the Executive Summary, respectively.

Based on the patient and physician-reported adverse outcomes, as well as the post-market reports of Restylane used in lip injection, please discuss the safety of Restylane injections for lip augmentation. Thank you.

DR. GALANDIUK: Is there anyone on the Panel who'd like to start the discussion or express concerns about safety? Dr. Miller.

DR. MILLER: Thank you. Michael Miller.

I think that the studies have done a pretty good job laying out

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the different adverse events that can happen, but they're self-limited and they didn't seem to affect the patients' satisfaction with the procedure. They seemed to accomplish what they wanted to accomplish with the injections, and most of them came back for further treatments.

So as long as it's clearly laid out, it seems like the patient is making this risk/benefit judgment and considering the benefits outweighing the risks, which is the definition of safety. So I think that it sounds like a safe material.

DR. GALANDIUK: Dr. Leitch, anything to add?

DR. LEITCH: No. Again, this is the weight of things, but clearly the preponderance of these effects are what you might anticipate to happen with an injection of a thing, and none of them appear to be life-threatening. And I think that the event of the death seems to be unrelated by that description. So I also think there doesn't seem to be adverse effects that would prevent use.

DR. GALANDIUK: Dr. Halabi.

DR. HALABI: I also agree with the previous comments, especially because those adverse events were resolved within two weeks. So I have no concerns.

DR. GALANDIUK: Dr. Newburger.

DR. NEWBURGER: I think these adverse events, as my colleagues have said, are expected and the important thing is communication

with the patient beforehand. If someone thinks that they're going to go out right afterwards and give a speech or go to dinner, that has to be communicated that this might not be a good choice.

And in terms of the adverse events, I think all of us who have done enough of lip augmentation, if you do enough, you're going to see them all, and I didn't see anything that was a surprise here.

DR. GALANDIUK: Dr. Mount.

DR. MOUNT: I think that the hyaluronic acid implantation has been thoroughly studied in the nasolabial folds, and I don't see any difference in safety and efficacy outcomes when in a different part of the face and the lips.

DR. GALANDIUK: Mr. Halpin.

MR. HALPIN: The safety profile appears to be very similar to what you see in the nasolabial folds, as was just mentioned. In addition, it's the exact same material that's been used since 2003, so I think there's a pretty good safety database overall for the product.

DR. GALANDIUK: Ms. Mattivi.

MS. MATTIVI: I think, as was mentioned before, the effects being fairly limited in duration, and as a physical therapist, when we talk about disabling side effects, I see that the duration of these is not a problem.

DR. GALANDIUK: Ms. Brown.

MS. BROWN STRONG: I would just add that there's nothing in

the safety data that I have seen that would scare me away, so to speak. I feel very comfortable with the data presented.

DR. GALANDIUK: Dr. McGrath.

DR. McGRATH: I agree in terms of local effects, which is really all that's referenced in this study, because -- in these studies, because that's all that happened in them. I have no concerns, but I do think that the other more serious rare effects have to be spelled out, because I think spelling out precautions and relative contraindications, based on the very things that you had as your exclusion criteria, has got to accompany this.

DR. GALANDIUK: Dr. Burke.

DR. BURKE: Well, I think I feel very reassured because the side effects are local, transient, they're not permanent, and there's less possibility of some unobserved side effect down the line because the implant is not absolutely permanent.

And the interesting thing to me is that most of the patients who -- and we know the cosmetic patients are among the most demanding patients that we have -- that even those that suffered side effects sometimes were, first of all, satisfied with the treatment and, secondly, very often had another treatment.

And we've had 14 years of experience in Europe and seven years of experience in the U.S. with this material, so we have a vast experience with it. And even more than the studies here, this has been used

off label quite a bit, so we would've heard of even other side effects if they existed.

DR. GALANDIUK: Mr. Melkerson, with regard to Question 1, the Panel generally believes that Restylane, as used for lip augmentation, is generally safe, despite the large amount of adverse events reported. However, the Panel does have some concerns about serious adverse effects and believes that these should be clearly listed on the marketing and labeling information.

Can we have Question 2?

DR. DURFOR: Question 2:

Moderate or severe adverse events occurred in 21% of the subjects that received less than three mL's of Restylane and 43% for the subjects that received more than three mL's of Restylane.

The relationship between Restylane dose and the incidence of moderate and severe adverse events was -- and we have a graph here that was previously in your Executive Summary -- and no clear relationship exists between injected dose in upper or lower lip fullness. And once again you've seen these slides as well.

Based on these outcomes, please discuss the clinical implications of injecting different amounts of Restylane in the lip, with a focus on the lack of correlation between injected dose and change in lip fullness, the risk/benefit ratio of injecting doses greater than three mL's in

both lips, and approaches for informing future physicians about appropriate injection doses should the product label cite -- and, for example, should the product label cite a maximum injected dose?

DR. GALANDIUK: A harder question. Dr. McGrath, why don't we start with you. Should there be a maximum injectable dose?

DR. McGRATH: Yeah, that was something I tried to think about. I'm not sure that the total maximum dose is the issue as much as the need for divided doses. And I would suggest that a way to approach this would not be to talk about a total maximum but rather the need for repeat treatment and divided doses without necessarily arriving at a final endpoint that gives a total dose.

DR. GALANDIUK: Is there concern about the lack of correlation between the injected dose and the change in lip fullness?

DR. McGRATH: I didn't feel that that was an area of concern.

DR. GALANDIUK: Okay. And I think you've already answered the part about the concern about injecting greater than three cc's.

Dr. Miller.

DR. MILLER: I agree with Dr. McGrath. I'm not concerned at all about the lack of correlation between the injected dose and the change in lip fullness. Because of underlying differences in everybody's lips, I would expect a different amount could be required depending on how much volume you need to change the lip shape.

I think that it is worth making sure that clinicians and patients understand that if they require greater than this three cc's, that the risk of adverse, you know, experiences is higher and a strong encouragement made to divide the doses. I'm not sure we have to say there has to be a maximum dose because, again, none of these adverse events are really dangerous or permanent; they're just unpleasant. So I think by telling people that the risk of an unpleasant experience is higher with a higher dose, I think that's important.

DR. GALANDIUK: Dr. Newburger.

DR. NEWBURGER: I think that the practitioners will figure out very quickly not to inject more than three cc's, except in extraordinary cases, at one setting because the patient will come back kind of angry that you can visualize the filler with these blue-gray deposits under the lip. And then you get into the whole issue of oh, my goodness, what are you going to do? And all you need is someone whose lip is swollen from a hematoma for an extended period of time. And that changes the state of the art, so to speak. Many people will need very small volumes because all they want is a little definition.

I think we're seeing more and more use of this in this off-label -- for this off-label purpose because the population is getting older and as the baby boomers are noticing perioral rhytids, the focus is going to also be on that area.

So I think that it may end up being a very small amount, and I think that the patient should be given an -- this doesn't belong in the labeling, but patients should be given an option to make an appointment two weeks hence, which they may keep or not, depending on how satisfied they are.

DR. GALANDIUK: Dr. Leitch.

DR. LEITCH: Yeah, my thing about the dosing, I think, really is related to this, because it's hard for me to believe it's not related to some of these cosmetic outcomes that I think look pretty adverse to me; but that, you know, if you do a smaller injection as that first injection and, you know, not exceed the three cc's, with the idea that there is that second visit for, you know, contouring or whatever, I think that's a way, and that's really my concern, actually.

And then, of course, in terms of a total maximum dose, I would say, well, how many patients received more than five cc's? I mean, if you haven't really tested, say, eight cc's, should you say that the side effects would be exactly the same and maybe would have some more of these complications of necrosis and that sort of thing if you got to sort of an outlier dose?

So I think there needs to be probably some upper limit for that first two-week injection time period that would be related to the number of patients that have received above a certain dose.

DR. GALANDIUK: Dr. Newburger.

DR. NEWBURGER: Excuse me, I have a question. I don't recollect, and I can't figure out which disk it was on, but isn't there a limit to the number of cc's that you should use at any given time with Restylane? On the insert.

DR. GALANDIUK: Could the Sponsor respond to that, please?

MS. LIN: And thank you, Dr. Newburger.

And I think there are two criteria for the treatment there. One is a recommendation not to exceed 1.5 per treatment per lip, and the second one is to treat the patients to the optimal correction there.

DR. NEWBURGER: I'm sorry, I mean on Restylane packaging as it is now, for the correction of --

MS. LIN: It's six mL.

DR. NEWBURGER: Right.

DR. GALANDIUK: So Dr. Leitch, can you summarize again what you were saying? So you don't feel that there should be a limit on the single injection dose?

DR. LEITCH: No, what I was saying is I think I would prefer the limitation remain at that three cc's for total dose for the first injection and then with the option to have a higher injection amount at the subsequent visit, the two-week visit. But I think there probably is an upper limit and we should -- I don't think you should say it's A-okay safe, if we don't have anybody who's been treated with eight cc's, to say, well, it's okay to have

eight cc's, because we don't have any data to say that that's, in fact, exactly the same side effect profile.

DR. GALANDIUK: Dr. Mount.

DR. MOUNT: I actually don't have any trouble with the lack of correlation between -- you know, it doesn't follow a dose-response curve, and that was my question, why this wasn't coming up as a drug versus as a device. I wouldn't expect a device to have the drug response curve. So I have no trouble with that.

As far as the current labeling and the recommendations, you know, I think that that's part of the learning curve, that's part of the education of the residents and future doctors that are going to be doing this procedure, and since the downside seems to be self-limited, I have no troubles.

DR. GALANDIUK: Dr. Burke.

DR. BURKE: In general, in my philosophy of life, I'm against excess regulation. But I think in this case, this material is going to be used by other specialists besides well-trained cosmetic surgeons and plastic surgeons and dermatologists.

So I think that it is important to have some limitation on the amount per lip per session, and I think the three cc's all together is not as good a kind of wording in a recommendation as an amount per lip per session. And maybe that limitation could be higher than the 1.5 cc's, but

maybe it should be something like the maximum that you've already observed to be basically safe. Maybe it could go up to 2 or even 2.5. But I think that recommendation is highly important for the substance because of the wide use that it will have.

DR. GALANDIUK: Dr. McGrath.

DR. McGRATH: I spoke once already.

DR. GALANDIUK: Oh, I'm sorry. I'm sorry. I called you. You have nothing to add based on the comments. I'm sorry.

DR. McGRATH: I have nothing new to add, then.

DR. GALANDIUK: Nothing new to add. Okay, good.

Dr. Halabi, I don't think we had --

DR. HALABI: Nothing new to add with regard the risk/benefits ratio, but as a point of clarification, this should be greater than or equal to 3 because if you look at the distribution, it's 56% of the 172 patients received less than 3 versus 44%. So as a point of clarification, it should be greater than or equal to 3.

I think, though, with regard to the lack of correlation between injected dose and change and lip fullness, I think this may due to the fact that you're dealing with a fuzzy endpoint, and this is, you know, beyond the discussion today, but I think it will definitely benefit the scientific community to work on making the endpoint more objective. But this is, again, beyond this meeting. So I concur with my colleagues on that. Thank you.

DR. GALANDIUK: Mr. Halpin.

MR. HALPIN: In terms of limits, I think given that each patient is different, I sort of -- I kind of like the concept that Dr. Burke was talking about, and thinking about that in terms of training rather than in terms of setting hard limits, particularly given that if you look at the data, there are some small n 's and some of the things we're looking at, n 's of 2 and n 's of 4.

And in some of the -- well, for instance, greater than 5, everyone seems to do well, but there's some issues in other areas, potentially. So I think maybe focusing a little bit on training or how to actually get people to understand where to go with this might be an option as well.

DR. GALANDIUK: Ms. Mattivi.

MS. MATTIVI: I think Dr. Burke has made some very good points about the widespread use that the product will be seeing. I think, also, the lack of the quantitative ability to measure change at this point also makes that difficult to talk about, you know, in terms of training and looking for a percent change as opposed to a volume limit is part of the consideration as well.

DR. GALANDIUK: Ms. Brown.

MS. BROWN STRONG: I appreciated the Sponsor's response -- it was this morning when we were talking in the volume discussion and the discussion was about the importance of the placement of the product. And

so I just want to put that out there with this because it seemed to me that we were being told that with proper placement, you got better results with less product, although the use of the product did ultimately or could ultimately depend on the size and structure of the patient's mouth.

DR. GALANDIUK: Mr. Melkerson, with regard to Question 2, it's hard to sum up. The Panel has no significant concern regarding the lack of correlation between the injected dose and the change in lip fullness. The Panel does not feel a need to cite a maximum injectable dose, but the Panel does have concerns in that they feel that the product will have widespread applicability to numerous types of physicians and possibly dentists, and feel that there is a need to set some type of limit for an individual dose per lip, if I read the Panelists' comments correctly. And that there should be training guidelines for physicians and users of this product, both in unit dose per lip or recommended unit dose per lip, as well as on application techniques.

Dr. Durfor, Question Number 3, please.

MR. MELKERSON: Before we go on, can I ask for a clarification?

DR. GALANDIUK: Yes, please.

MR. MELKERSON: You've talked about not wanting to put a limit in.

DR. GALANDIUK: The maximum.

MR. MELKERSON: Typically, we also consider precautions like the safety and effectiveness of use of a product -- has not been studied or

they've not had data, so that's another thought process that's not necessarily putting a hard limit on, but you can basically address, potentially address, that with a precaution.

Would that be something that the Panel thinks would be worthwhile based on -- and I think there were a couple comments made of we have data up to --

DR. GALANDIUK: Five.

MR. MELKERSON: -- five, but we don't have any data beyond five.

DR. GALANDIUK: Dr. McGrath.

DR. McGRATH: The only thing, I think, that you'd want to be careful how you word it so that it's accurate. I mean, actually, the data might be up to whatever it is. Two and a half per lip per treatment is more specific, and that would be more accurate than saying five because someone might think that's over the lifetime of the product or something like that whereas we're really just talking about one treatment, one lip, and that might be more reflective.

MR. MELKERSON: Thank you.

DR. DURFOR: Question 3: Please provide comment on the following patient populations that were underrepresented in the study.

The study enrolled four patients under the age of 22 years.

Please discuss the appropriateness of Restylane lip augmentation in patients

under the age of 22. For example, does this patient population (seeking lip augmentation rather than restoration of lip appearance related to aging) raise any safety or effectiveness concerns that warrant additional pre-market study?

The study enrolled 38 persons with Fitzpatrick Type IV and 3 patients with Fitzpatrick Type V, and no patients with Fitzpatrick Type VI skin. Product effectiveness assessments were based on 31 Restylane and 10 no-treatment patients in this subgroup. Please comment on the safety and effectiveness of Restylane for lip augmentation in this patient population and whether any safety or effectiveness issues warrant additional pre-market study. Such considerations may include the data collected in the pivotal study, a previous study of 150 subjects with Fitzpatrick IV, V, and VI type skin that received Restylane and Perlane injections in the nasolabial folds.

And then (c): The study enrolled 179 female and 1 male patient. Please comment on whether lip augmentation in men raises any safety or effectiveness concerns that warrant additional pre-market study.

Thank you.

DR. GALANDIUK: Okay, start with Dr. Halabi. First three questions. First, the young people --

DR. HALABI: Yeah, okay. For the statistician.

DR. GALANDIUK: -- Fitzpatrick and then men.

DR. HALABI: Okay. Well, as a statistician, I definitely would say

you cannot make inference based on the younger patient population. I would have liked to see more data, but since the sample size is only four, that may raise some concerns on the effectiveness. Although I think it will be very close to the general results, but we can't even make that statement because it's based only on four patients.

And then the same thing with the Fitzpatrick type IV and V, again, the sample size was either very small, less than a handful, or missing for the higher scale, so again, I think there may be the need to do more data collection before you can generalize this to the general population, and definitely with regard to gender, since the majority of the patients were female, you cannot really generalize to the male population.

DR. GALANDIUK: And you don't feel the nasolabial fold population is adequate for the Fitzpatrick darker skin types?

DR. HALABI: Yeah, I said that I don't think it is.

DR. GALANDIUK: Okay.

DR. HALABI: Thank you.

DR. GALANDIUK: Dr. Miller.

DR. MILLER: Thank you. Michael Miller.

I think that even though the data are limited for these subpopulations, it's hard for me to, sort of, conjecture about why they would behave differently. And before I would, you know, insist on a special study looking at these different populations, I would like for someone to explain to

me some hypothesis of why you might see some different performance in these people, and I can't imagine that at this point.

So I think that we don't have the data, so there is some question perhaps that can arise, but I think I'm comfortable with what we've seen for the people we do have good data for, that it would probably apply to these other groups as well.

DR. GALANDIUK: And you feel the nasolabial folds data is sufficient for the Fitzpatrick darker skin types?

DR. MILLER: Yes, I do. The differences there would be depigmentation and keloid scar formation. These are the different performance, I would expect, that this hasn't been seen and we don't know exhaustively that that's not going to be seen, but I think we can be confident enough, based on what I see here, that it's -- I don't think a special study would be necessary for this.

DR. GALANDIUK: Dr. Newburger.

DR. NEWBURGER: I see a potential actually for a complication that could occur in younger people, which is that when someone is under the age of 22 years, the desire to have lip filler is -- it's different. It follows a fashion, if it's not JLo or Beyonce, then who is going to be the next ideal.

So these lips are firmer, there's more subcutaneous tissue, there's certainly more fat. And so the filler is going to be under more stress, the tissue's going to be under more stress than would happen if you were

injecting an aged lip with the same similar quantity, in my opinion.

And my question is without seeing overt scarring in your study period, isn't there, in fact, more fibrosis? I would expect to see fibrotic changes occurring, not necessarily in six months but maybe over the course of a year or so. And it's certainly been my experience that when people have had multiple injections with filler, whatever they are, just the fact that the lip has been needled, whether it's antegrade or retrograde, that there is more difficulty in threading the filler in an even fashion, it takes more care.

And so I'm wondering about this. I don't think it's a contraindication. I think that, in general, the safety appears to be no different, but that is something to consider down the line because you're addressing a different problem, in my opinion.

I think that there is adequate data in terms of Fitzpatrick type IV, V, and VI, particularly in light of the larger nasolabial folds study, to feel comfortable with its safety. And I don't think it's going to be very easy to get male patients for a study who want to have fuller, poutier lips, so I don't see any reason that they would be excluded, but I don't see any particular safety or effectiveness problem.

DR. GALANDIUK: Dr. Leitch.

DR. LEITCH: Well, other than I really don't like people that young to be doing these things to themselves so early on in life, so it's a philosophical thing, but you know, this issue of is it possible that over a long

period of time there is scar formation that could alter the appearance, to some extent, at an earlier point in life. As you get older, people accept that more than they might accept in the ages of 20 to 30. So I think there is a possibility that a longer-term outcome might not be as ideal in this patient population and, you know, we don't know that, basically, because not many people have been observed in that category.

For the Fitzpatrick type IV and V, I was pretty convinced by Dr. Few's discussion, and I think the other study gives us some data for it. I'm actually astounded that there is not the effect on that skin, and I guess the issue of keloid, I'm assuming, from the nasolabial fold, there's enough follow-up that long-term, that's not been an issue, either.

And I kind of agree about the men thing. You know, they can have it, if they want it.

(Laughter.)

DR. LEITCH: But trying to do a study for them is probably not going to be very fruitful.

DR. GALANDIUK: Dr. Mount. I value your remarks about the pediatric group.

DR. MOUNT: Well, I think that the statistics and the study design, we really can't say anything about children and we really can't say anything about the subject who is not -- had complete skeletal and facial maturation. And so in that group, in particular, I think that we, just based on

the data that we have, I think we need to exclude them from routine use.

That being said, there are many, many indications, particularly in my practice, where I can see this could be very, very helpful. I treat a lot of children with congenital lip anomalies. So I think that that data is worthwhile getting, but I would not use it off-label on a skeletally or a growth-immature person based on the data that we have.

Regarding the Fitzpatrick IV, V, VI population, I had asked the question earlier, and I forgot to bring it up the second time around, you know, how many people actually constitute an adequate number to give you the power to say that there is no difference in outcome from Fitzpatrick I, II, III versus Fitzpatrick IV, V, VI. And I welcome some more information about that before I could really make a comment on that.

DR. GALANDIUK: Would the FDA like to comment on that?

MR. MELKERSON: Go ahead.

MR. VAN ORDEN: Do you just want to restate the question again? The power to?

DR. MOUNT: Let me put it in the context of the background of why I asked this question. Whenever I'm making a new study, we always meet with a statistician before even designing the study so that we have the adequate number of subjects to get the adequate number of power to really make the statements that we are expecting the data to produce.

So my question is, looking back at it, if we are comparing that

there are no differences between the Fitzpatrick I, II, III versus the IV, V, VI, how many do we need, how many subjects need to be studied to see that that population reacts exactly the same or has no difference statistically from Fitzpatrick I, II, III?

MR. VAN ORDEN: I don't know. The assumption is that there is no difference.

DR. MOUNT: I think that's the assumption that we're sort of making here, as a panel, but there is no difference between the untoward effects of I, II, III versus IV, V, VI.

MR. VAN ORDEN: I guess, from a statistical point of view, we say -- we use, within -- there's not going to be, like, a non-inferiority margin or we say -- we can't say they're exactly the same, but we can say that they're not going to have more than, say, 6% more adverse events than you would see in the normal population.

So based on what we've seen, based on these 40 patients, and not having seen these certain adverse events, I would estimate that the rate of adverse events in these darker skin types is no more than 8%. So again, certain adverse events, if you want to talk about a specific adverse event but an adverse event, say, that has -- it happens in 6% of the time, to have a 6%, then, margin of error to say it's less than 12%, we'd need 88 subjects.

I don't know if that's getting at what you're saying. But we would have to talk about specific adverse events, and we'd never say that

they're exactly the same, but we could say they're within. We'd have to define a margin. And we can nail that down, if you just want to. We can negotiate that with the Sponsor, if you think there's a specific margin of error that you would comfortable with.

DR. MOUNT: I'm not trying to trip you up, I promise.

MR. VAN ORDEN: Right, I understand.

DR. MOUNT: But the concern would be --

MR. VAN ORDEN: There are lots of things to consider to see.

DR. MOUNT: -- that it is a small end.

MR. VAN ORDEN: It is.

DR. MOUNT: And to use that end and sort of globally say, well, the two groups are going to react the same or have the same risk of adverse events, I think, is a little premature to make that assumption that those two groups are the same based on the end that was presented in the study. So for that aspect of things, I would be cautious.

MR. VAN ORDEN: Okay.

DR. GALANDIUK: Would the Sponsor like to comment?

DR. FEW: Before I begin, I could talk about this for about an hour, but I promise I won't. A couple of thoughts, and this is based on literature: the one paper I published and then probably a dozen others on the subject.

Really, if you look at the study, looking at the nasolabial fold on

150 subjects, there is roughly 5, little more than 5% incidents of temporary or very transient hyperpigmentation. In my practice -- and I think this is where education comes in; it's really the reason why this indication needs to pass, in my opinion, is in different pigmentation groups, you see different pre-treatment findings.

So as an example, for the nasolabial fold, you often, especially in a deeper fold, like a Type III or IV fold, you will often see, at the base, hyperpigmentation. Once you fill that, you see hyperpigmentation post-treatment and you think oh, I caused this; but in reality, you have not. And so it really does fall into a category, and this is, again, I just wrote in Fo Edna Hize's (ph.) textbook on aesthetic plastic surgery on ethnic skin groups. This is something that I teach, and it's an important factor, and I think having this indication would help, I think, to potentially avoid some misunderstanding on this area.

Another point, I think, that's really important to make, and again, I'm not a statistician but we did look at the power to answer your questions, specifically, based on the n that we have in the study with an assumption that there's a 5% incidence of having this transient problem. There's an 86% likelihood that we captured that problem in this study.

So really, could have said another way, if you added maybe five more patients, then you move it up into the high nineties, but is that really going to make a difference in terms of something that is transient, at best?

Probably the last point, which I think is incredibly important and a point that was brought up, is injection technique. This is something that I emphasize, going back eight years, that when you're injecting darker skin, you have to inject it differently. You have fewer perforations to the skin, you're injecting deeper to avoid potential inflammation at a more shallow level.

So this is, again, educational, and I think that, in that case or in the study that looked at 150 nasolabial fold subjects, there are a lot of factors that fall into this and I think, big picture, you really -- the idea of doing another study to look at lip enhancement in a group that tends not to seek out lip enhancement, it doesn't make practical sense. And I think that you're probably unfairly penalizing a group for the sake of a statistical fantasy, if you will.

And as I look at this, you know, really, this is not normal versus normal. Forgive me for taking a bit of offense with that. But it's more of a group that has been historically underrepresented in terms of clinical trials, and I actually applaud the FDA because now this is being looked and I actually am personally very appreciative of that.

So please don't hear it any other way, but I think, really, if you look at this carefully, there are a lot of factors that really go along with what Dr. Miller said, that intuitively there's little reason to assume that there's going to be a problem here, and so, I mean, relative to all the data that we

have and patients who we've treated, so I tried to keep it as tight as I could.

DR. GALANDIUK: Mr. Melkerson.

MR. MELKERSON: Just a subtle but important point. The question, as phrased, is pre-market. In other words, do I need this pre-market to make a recommendation? Later on you'll be asked about post-market, so some of these issues could be looked at in that context, if it's not needed to determine the risk/benefit ratio or the safety and effectiveness of the product for its proposed intended use. But some of these questions may be subject, and if you go back to the question of post-market studies, that may be -- so I just want to make sure that was brought into your discussion.

DR. GALANDIUK: Thank you. Dr. Burke.

DR. BURKE: I think Mark just said a lot of what I was going to say. I don't think that not having studied these subpopulations in more depth is at all a limitation to approving an indication for lip enhancement. As far as young people, we already have so many adults who come back for repeat treatments and all of us that do these implants, any kind of soft tissue implant, know that often patients come, return, more than we would want them to return for extra implants, so -- and I want to stress, of course, that this is not a permanent implant.

It's not that we're putting more and more of something that will remain forever, like silicone, into the lip. So I can't imagine that there are many long-term complications. And you see the result of everything before

you would do another treatment. So I can see that there are possible -- there might be -- there are indications for some individuals under 22 years old, particularly, who might've had some traumatic event that affects the architecture of their lip.

I think, as far as addressing the skin types IV, V, and VI, often we don't see possible -- although no complications were seen in about the 30 patients looked at of the 31 Restylane patients, if there might be a chance of keloid formation or extra fibrosis, we'll see it when more and more people are treated, and that happens for every medication and every kind of implant.

When you have a very large population may be getting it, because the indication is known publicly when it is an FDA-approved publication, we would see that complication and be able to collect post-approval data on this.

And also stated, this population doesn't usually seek lip enhancement, and it's the same with the male population. I can't see a difference in anything different physiologically for this indication for Restylane in a male population versus a female. So, basically, I don't see any of these -- of not having more data now is a limitation to approval, but I think that, in fact, approval will result in our being able to collect a lot more data on these subpopulations.

DR. GALANDIUK: Dr. McGrath.

DR. McGRATH: I think Dr. Burke said that well. I'm going to go

backwards. I agree with you. I don't think there's any necessary additional pre-market study that needs to be done on the question of male patients, nor do I think there is such required for the high Fitzpatrick number patients. I think Dr. Few's comments are helpful, and I think the previous work and demonstration of effectiveness and safety in the nasolabial crease makes that unnecessary to do anything additional.

The one I struggled the hardest with is the people under the age of 22. In answer to the question before us, I don't think additional pre-market study is necessary to rule on the safety or effectiveness of the product. I don't have concerns about it mainly because, as Dr. Burke just said, we have a long history of patients who have had this product over and over, certainly in other parts of the face, and we know that there's no additive effect that we're aware of.

But I don't want to be paternalistic, and I do believe in patient autonomy, but I'm really troubled with the concept, as Amy said, of people, very young, doing a lot of lip enhancement. And I don't know -- that's really not answering this question, which -- but I think it's something that we -- I think we could bring this up, that I'm troubled by seeing 16-year-olds, for example, perhaps using this product for this purpose.

Many of us on this panel have sat here with another device that was creating a lot of problems with very young teenagers who were overusing a product, and I wonder, you know, I just don't know whether there should

be an age limit perhaps for it, 16, I don't know. I assume that since this is an injectable, we would have to have parental permission because it's a procedure under the age of 18; someone would have to have parental permission to have this done. I think I would do that in my practice because it's an injection.

But, again, I don't even know if that's sufficient, so I don't know if this is even appropriate to bring it up, but since I first realized what we were talking about, this has been bothering me, and I really haven't yet come to a conclusion because, again, it is paternalistic to decide that there's an age cutoff where something is wise or not wise for someone else, but it is -- it bothers me.

DR. GALANDIUK: Now, it's very appropriate for our patient representative, Ms. Brown, to make a comment.

MS. BROWN STRONG: First, I'll say that as far as pre-market data goes, I'm satisfied with what is there, but I will address what several people have talked about and that being the patient population, which it's almost different patient populations and different intentions of results because when you're talking about an over 40 population, it's really rejuvenation.

And if you're talking younger than that, it's enhancement and then, I guess, there's also the indication for -- and I don't know the proper terminology -- to correct defects, you know, so you've got augmentation for

different reasons. And I think that's pertinent because I do think -- I was very interested in what the doctor said about, you know, what does it do to the structure of the lip in someone who is very young. But really, I think, the largest patient population is, you know, the female over 40 that's really seeking rejuvenation versus extreme enhancement. I think that's all.

DR. GALANDIUK: And, Ms. Brown, can you comment briefly about the Fitzpatrick, the darker skin type patients, and the male patients?

MS. BROWN STRONG: Well, I do agree that that's going to be a very difficult population to study pre-approval. I think, in time, you may grow that population, but again, it's not going to be for the same reasons. It's going to be, you know, enhancement or to correct a defect, most likely, as opposed to revitalization piece.

DR. GALANDIUK: Ms. Mattivi.

MS. MATTIVI: I would agree with everything that was just previously said. Again, very troubled by the younger population and the potential differences in the skin, itself, as opposed to the aging population, which I include myself in, but I'm beyond that. As far as the pre-market for the Fitzpatrick skin types and the male population, I'm satisfied with the data that have been presented.

DR. GALANDIUK: Mr. Halpin.

MR. HALPIN: If you look at other dermal fillers that have been approved for other indications, I think that the study data population they

have is appropriate for approval.

With regard to the Fitzpatrick skin color IV, V, and VI data, the only other thing I wanted to add is that in addition to the Sponsor's study, other manufacturers of HA dermal fillers have also studied this group in a similar size and fashion and gotten very comparable results, so I think there is a robust dataset out there that says that HA dermal fillers are appropriate for that safety point.

DR. GALANDIUK: Mr. Melkerson, with regard to Question 3, the Panel -- I will start with the easy parts first. The Panel generally believes that no additional pre-market studies are necessary regarding the Fitzpatrick darker skin types or regarding lip augmentation in the male population.

However, the Panel had serious concerns regarding the younger population, the age 18 through 22. There were serious concerns regarding possible occurrence of lip fibrosis with repeated injections, although panelists did bring up the comments that repeated injections of Restylane have been performed with safety in many populations. However, there were concerns that this population should be seeking lip enhancement for, perhaps, the wrong reason.

Is that satisfactory?

MR. MELKERSON: That's satisfactory, but I just wanted to make one clarification.

I've heard discussions that you were talking about a lot of off-

label use. You have to make sure that you're basing it on what's currently in the PMA submission. Your knowledge base will help us, but that may mean that the Sponsor has to do -- provide the literature in supporting those statements. So I just want to make sure people are focusing on data that's presented within the PMA.

DR. MILLER: Can we pause, Madam Chair?

DR. GALANDIUK: Yes.

DR. MILLER: Before we move on from that, I just want to make sure I understand what you've summarized us to say. And what we were saying, we have a philosophical problem with it, and I agree, I'm uncomfortable with this, but that really has not anything to do with the safety and efficacy.

DR. GALANDIUK: No, it's just saying do we need more pre-market studies, and I don't think anybody said we need more pre-market studies, but we have serious concerns whether or not the label should say not for use in patients under 22.

DR. MILLER: Okay, so just a comment about using under 22 years old, but not requiring more pre-market studies or further data or anything like that.

DR. GALANDIUK: Correct.

Mr. Melkerson, is that adequate?

MR. MELKERSON: That was my understanding of what you

were saying, yes.

DR. GALANDIUK: Okay. Well, we're now going to take a break, our 15-minute break, until 3:15. And, again, Panel members, as usual, please don't discuss the meeting topic amongst yourselves or with any member of the audience. And we'll resume at 3:15.

(Off the record.)

(On the record.)

DR. GALANDIUK: We're having a little technical difficulty here, so I'll ask Dr. Durfor to read his question slowly, and as soon as the monitor is up, we will project Question Number 4. And they also should be in your handout.

DR. DURFOR: It will be up in a short moment. So let me go ahead and read these questions, and then you can come over and enter in the password for the projector. Thank you.

The percent of treatment responders, as judged on the MLFS by blinded evaluators, treating investigators, and independent photographic reviewers are presented below. And you'll see that in a minute on the slide. The levels of agreement for these decisions are reflected in the reported weighted kappa statistics. I think we're getting there. I'm very slow.

The absolute change in MLFS from baseline for upper and lower lips at Week 8 as determined by blinded evaluators were presented in Table 7 of the Executive Summary addendum. Based on these data and other

information presented in the PMA supplement, please comment on the effectiveness of Restylane in lip augmentation and please comment on the most appropriate method for describing product effectiveness in the product label.

DR. GALANDIUK: Dr. Halabi, why don't we start with you? Can you comment on the effectiveness of Restylane? Are you satisfied that it's effective as shown by the pre-market data?

DR. HALABI: Yeah. I mean, if you think a 1 point change increase is clinically meaningful and based on the observed data it was 2, then I think it is definitely effective. Although, I have still some problems with the primary endpoint because I believe it's still -- it's a bit fuzzy and not objective.

And based on the data, it seems that the blinded live evaluator and the treating investigators had high response, although I'm really concerned about the independent photographic reviewers. So I'm tempted not to use that as part of the product labeling.

DR. GALANDIUK: What would you use?

DR. HALABI: I would definitely suggest the treating investigator or the blinded evaluator, although again, the agreement really was pretty bad, but at least with the exact agreement of 51% and 57 was, I guess, the best. So I would definitely go with the blinded or the treating investigator but not with the IPR because there are problems with that.

DR. GALANDIUK: Now, because this would be as a product label, there wouldn't be a blinded investigator, so it would be the --

DR. HALABI: The treating physician, right.

DR. GALANDIUK: -- treating physician would evaluate. Okay.

DR. HALABI: Thank you.

DR. GALANDIUK: Thank you. Dr. Miller.

DR. MILLER: I think that the difficulty in this measuring scale confirming the effectiveness has more to do with the inadequacies of the methodology than anything else. And I think I'm satisfied that the Restylane effectively augments the lip, so --

DR. GALANDIUK: What kind of method of describing product effectiveness should there be in the product label? Should they describe the MLFS, should they -- what should they do?

DR. MILLER: I think that would be fine. I mean, I think most people who do this type of work understand the difficulty in really -- because of the suggestive nature of the outcomes. It's very hard to do a nice, tight study which confirms the outcome, so -- but I think you could take -- I don't have a strong opinion as to what pieces should be used. I think any part of it that makes sense to the FDA.

DR. GALANDIUK: Dr. Newburger.

DR. NEWBURGER: I agree that Restylane is effective in lip augmentation. I think that the Medicis scale should be mentioned, and I

think that it's appropriate to list the treating investigators. And I think that it could be mentioned that improvement was also found with the following methods. But is this where we would -- I think the global improvement scale should be included, as well, because I think that that's also important with how to describe product effectiveness, with the subjects it was effective.

DR. GALANDIUK: So describe all the methods that have been used in pre-market data?

DR. MILLER: Yes, in microfiche.

DR. GALANDIUK: Okay. Dr. Leitch.

DR. LEITCH: I agree that it's effective for augmentation to a certain time period, which is -- I don't know if we'll get to that but, you know, to say for what time period it seems to be effective. And as far as the evaluators, I do think the blinded live evaluator still has some value; it's just they didn't see the pre-photos for the no-treatment group, so you know, I think that difference is -- it has an explanation, but I think it looks like they're pretty valid as compared to the photo group, so the blinded live and the treating investigator would be the ones most cogent. So those are the things I would say.

DR. GALANDIUK: Dr. Mount.

DR. MOUNT: I would also agree that Restylane is effective in lip augmentation and then on the -- describing product effectiveness on the product label, I think that it should be labeled specifically that the

effectiveness has not been established in children.

DR. GALANDIUK: Dr. Burke.

DR. BURKE: Well, I agree that this is effective for lip enhancement, and I think that it might be possible, all that anyone can do when looking at photographs -- and the blinded investigator seeing the patient looked at the pre-photograph, and even we, as physicians, when our patient comes, we rely more on the photograph than our memory because we all have so many patients and it's impossible to remember the details of everyone's face to the extent that you would want.

So I think that the blinded observer and the photos are the best, and I think that since you already have the possibility of looking at the footprint of the improvement from the photographs -- I mean, that would be just tracing the size of the lips -- I think that would be interesting to do because that, at least, would be something that is quantitative.

You can't tell the volume because you can't see the depth and measuring that depth is very, very difficult because I've done those studies with small wrinkles and it's -- I think the main thing is that we all agree or most of us here agree, I certainly do, that we do see improvement and -- but I think that you have the possibility of doing something quantitative, which would at least be of interest in the medical literature and the technology of doing that might be of interest for future studies for other kinds of implants and even other indications.

DR. GALANDIUK: Dr. McGrath.

DR. McGRATH: I think that the effectiveness for lip augmentation has been established.

DR. GALANDIUK: And regarding what assessments, what methods for describing product effectiveness should be listed in the product label?

DR. McGRATH: The only one that we really have that's in place is the MLFS, and I think using something of that nature. To go beyond that becomes very difficult because asking others to gather photographic data that would be matchable or usable as part of the product use requirement would be very difficult, so I think you can only use what exists and that's the -- currently, the LFS. Thank you.

DR. GALANDIUK: Okay. Ms. Brown.

MS. BROWN STRONG: I also agree that it is acceptable, that it does what it's supposed to do. And I like the use of the MLFS. I have to look at it because I keep forgetting what the letters are. But I like that because I think that communicates to the patient as well as to the physician and gives people an opportunity to have a reasonable expectation, understand what that is.

DR. GALANDIUK: Ms. Mattivi.

MS. MATTIVI: I also agree that the effectiveness has been established and that the use of the MLFS should definitely be included. It's

such a subjective outcome and a subjective assessment to a certain degree, and for the patient to have that information and to know for themselves how this is going to be assessed, I think, will be helpful.

DR. GALANDIUK: Mr. Halpin.

MR. HALPIN: I think that the two-point difference shown on the treating investigator and the blinded evaluator MLFS scale shows that the product is effective. In terms of what you put in the labeling, from an industry point of view, I would stay away from photographic assessment and go with live evaluations because there have been studies that show that the photographs tend to compress or diminish the treatment effect, and most sponsors are moving toward studies where they're actually using live assessments as their primary endpoints.

DR. GALANDIUK: Thank you.

Mr. Melkerson, with regard to Question 4, the Panel generally believes that Restylane has been shown to be effective in lip augmentation.

Regarding the second part of the question on the most appropriate method for describing product effectiveness in the product label, there was a significant variance among the Panel members since many thought that the methods of assessing this were subjective.

The majority of Panel members, I believe, thought that the MLFS was a good score to list for assessment of product effectiveness and others thought that validation by -- assessment by the treating physician

would be good. Other Panel members thought that all three grades, methods of assessment, should be mentioned.

Is that adequate, Mr. Melkerson?

MR. MELKERSON: Yes, thank you.

DR. GALANDIUK: Could we have Question 4, please,

Dr. Durfor?

DR. DURFOR: Question 5.

DR. GALANDIUK: I'm sorry, 5. Sorry.

DR. DURFOR: Should FDA determine that the pre-market data demonstrate product safety and effectiveness, and appropriate risk/benefit profile, there are some potential post-market questions that need to be addressed. The Panel will be asked to discuss and comment on the appropriateness of the following possible post-approval study questions.

So here is Question Number 5: The pre-market device performance data from the study reflect single Restylane treatment sessions in 172 patients and a repeat Restylane treatment session at Week 24 in 93 patients. Please discuss whether a post-approval study is recommended to evaluate the safety and effectiveness of multiple Restylane treatments for lip augmentation. If so, please comment on the safety and effectiveness endpoints that should be assessed, the inclusion of specific patient populations, the duration of patient follow-up, and the study design.

Thank you.

DR. GALANDIUK: Why don't we start from the other side of the room?

Mr. Halpin, do you think that a post-marketing study would be necessary to assess repeat injections?

MR. HALPIN: I think, given the extensive history of Restylane in nasolabial folds and the fact that at least half the patients were studied with repeat injections, I wouldn't necessarily, from an industry point of view, think that a post-market study would be required.

DR. GALANDIUK: Thank you. Ms. Mattivi.

MS. MATTIVI: I would agree. I don't see the reason at this time for a post-market study.

DR. GALANDIUK: Ms. Brown.

MS. BROWN STRONG: While I think it might be interesting and a benefit for optimal use and optimal benefits, I don't think it's necessary for safety or effectiveness.

DR. GALANDIUK: Dr. McGrath.

DR. McGRATH: I'm having a little trouble answering this because I think we're missing a question. Question 4 was comment on the effectiveness of Restylane. We never got a Question 5, which was comment on the safety of Restylane for lip augmentation. Instead, that's kind of rolled into the question of whether you want to do a post-approval study, which I think changes the complexion of that question a bit.

DR. DURFOR: I appreciate your question. I believe safety questions were posed earlier and we moved from safety into effectiveness. So if we look at issues of Questions 1 and 2, they were safety questions, and then you'll have a voting question that will revisit the safety question again. That was the intent of the way these questions were laid out.

DR. McGRATH: Okay, thank you for clarifying that. The reason I made that comment is I think there are some open-ended safety questions that have to do with the very rare serious adverse event type of thing, and I think we have to put those out on the table and somehow that information has to be collected.

But that having been said, the very common adverse events are very -- are temporally limited and they're not -- they don't appear to be permanent deformities or problems. So in my opinion, that takes the need for a formal post-approval study off the table, but it doesn't take away the need for somehow capturing the information about these rare serious adverse events.

I'm talking about the angioedemas and things of that nature that will presumably come up when this is done more openly and more commonly. And, specifically, I don't think you need a post-approval study to include more of any of the specific populations.

DR. DURFOR: Thank you.

DR. GALANDIUK: Dr. Burke.

DR. BURKE: I don't think we need a post-approval -- I don't think we need a pre-approval assessment of the subpopulations, but I think it -- and I don't think we need a post-evaluation, a formal one, but I think it's certainly of interest if data can be collected and if the patients already studied could be followed even for a year or two. It would be certainly of interest.

DR. GALANDIUK: And, again, the question here assesses -- to evaluate the safety and efficacy of multiple Restylane treatments, so that's specifically what this -- such a post-study would be regarding.

Dr. Mount.

DR. MOUNT: I think that a post-approval study, in my opinion, should be done on the specific patient population of use in children. Of children, of skeletally immature children, if they get multiple Restylane treatments for lip augmentation over their lifetime, I think that is a group that should be kept on the radar.

DR. GALANDIUK: And with respect to the different points there, the endpoints that should be assessed, the duration of follow-up and study design, could you comment briefly on those?

DR. MOUNT: Yeah, the duration of follow-up would be very difficult because it would depend on what time the child would be potentially exposed to Restylane. If it was during teenage years, I would think that five or ten years would be adequate. If it was a four- or five-year old, I think that

should be longer. But I don't have any data to support how long you should follow someone if you did a Restylane injection on someone who was four or five.

DR. GALANDIUK: Dr. Leitch.

DR. LEITCH: I guess I would favor a registry-type approach of people receiving multiple treatments. I guess you could say well, we "know that" from the nasolabial fold data but, you know, whether or not the submucosal injection might turn out to be different with multiple injections, you know, I think is a question. And I would feel it probably most strongly for the younger patients, and what I would say would be, for younger patients, probably a five-year duration of follow-up, for older patients, more like a two-year period of follow-up.

DR. GALANDIUK: Dr. Newburger.

DR. NEWBURGER: I would like to see a small study done of young people.

Is between the ages of 18 and 22 not skeletally developed yet, Dr. Mount?

DR. MOUNT: Del Mount.

I think that, by most people's standards, over 18 would be considered skeletally mature.

DR. NEWBURGER: Okay. My understanding, then, is that that would be for a completely different purpose. In other words, younger, you're

looking to repair a defect which was not in the purview of this study rather than esthetic enhancement in people who had scarring or severe asymmetry or other anatomic problems were excluded.

I'd like to see, though, 18 to 22-year-olds studied, and I'd like the follow-up to be one to one and a half years if they get repeat treatments. But that's a very -- it's very hard to capture that patient population.

The other issue that I have in terms of a registry, we went through this in great detail when we reviewed Sculptra in maybe 2003 or 2005; I can't quite remember. Then we seriously put on a registry and limitation of access to this product to the HIV-positive population because it was presented with very minimal data and the company had said it wouldn't be marketing for the non-HIV population. But because of some issue with CDRH's ability to do this, it wasn't possible.

Is that correct, Mr. Melkerson, that CDRH can't enforce a registry or limit access?

MR. MELKERSON: Limiting access, once it's marketed, you're marketed. It's the states who limit who can use the product. But in terms of a registry, it's what does the registry mean in terms of a post-approval study, and I would defer back to our post-approval study group, if they're still here.

DR. NEWBURGER: And with 2.6 million units being used worldwide, I don't think that we're going to get that, so it would be wonderful to have a follow-up study on the young population, but I don't know that

that's possible.

DR. GALANDIUK: Dr. Miller.

DR. MILLER: Yes. I don't think we need a post-approval study, and I think some of the questions raised about children -- not children, people 18 to 22, they're good questions and we don't have data, necessarily, to answer them. But simply not knowing doesn't mean we don't know anything.

I mean, we know -- there's a lot of experience with this material, and just because you don't have data for that specific population doesn't mean we can't make any comment about it, and we'd have to have a good reason to think they would behave differently, and I'm not sure I have a good one. It may be something that professionally we can study, but I'm not sure it needs to be done, like, through the FDA post-approval mechanism, you know, just some --

DR. GALANDIUK: Dr. Halabi.

DR. HALABI: I think it will be good to have registry on the younger patients, and I would like to look at, in addition to MLFS, if it's possible to include more validated endpoint. And I think this is going to be a little bit more in Question 6, so a validated endpoint is not as subjective, so I think that's really important and we'll advance the field forward.

DR. GALANDIUK: What endpoint would you suggest?

DR. HALABI: This is really not my area, but I don't know. I mean, it may be worth validating the one-unit increase. I mean, that may be

an endpoint that the Sponsor may consider looking at, validating the endpoint to a wider practice. I believe it was based on five physicians. Something that makes all the surgeons comfortable with that endpoint, that there's no ambiguity, so -- and if possible, to take into account the duration of response because that's really missing in the endpoint.

DR. GALANDIUK: And what duration of follow-up would you --

DR. HALABI: I think two years seems -- again, in the absence of data, it's very hard to make these decisions, but it seems two years is a reasonable timeframe.

DR. GALANDIUK: Mr. Melkerson, with regards to Question 5, there is -- difficult to make consensus with the Panel's recommendation.

The majority of the Panel do not feel that a post-marketing study is required. However, several individuals in the Panel believe that a registry should be created to follow outcomes in individuals receiving repeat -- specifically, a registry created for specific populations, namely young adults between the ages of 18 and 22.

Two Panel members did feel that a post-marketing study would be indicated for that same population of 18 to 22, and one of the panelists specifically said that a study in young children and the follow-up times would differ depending on what age the child would have. For example, teenagers would demand, perhaps, a shorter follow-up than young children, which would demand a longer follow-up, and those children would have a different

indication than lip augmentation for cosmetic reasons. Those would be more for correcting of defects.

So difficult to sum up the recommendations of the Panel regarding that.

MR. MELKERSON: That's acceptable. Thank you.

DR. DURFOR: Question 6: Regarding future studies of dermal fillers for lip augmentation, Attachment 1 to the Sponsor's executive summary presented the 5-grade lip fullness scale for upper and lower lips. As discussed above, a high level of agreement between blinded evaluators, the treating investigators, and independent photographic reviewers was not observed. Based on your clinical training and experience, please comment on approaches that future studies might employ to improve measurements of device safety and effectiveness in lip augmentation. For example, please comment on:

- a. Which assessor provides the most accurate evaluation of patient outcome?
- b. What role should patient evaluations play in determining clinical safety and effectiveness?
- c. What issues should a sponsor consider when developing a metric for evaluating effectiveness in lip augmentation?
- d. How might a sponsor determine the magnitude of a change on a lip appearance scale that correlates with a clinically significant result?"

Thank you.

DR. GALANDIUK: And realizing that not all panelists will have equal things to contribute since this is largely a clinical question, Dr. Halabi, would you like to comment on any of these?

DR. HALABI: Again, I'm not a clinician, so as a statistician, I can tell you my wish list; whether it's practical, that's another story.

Based on the data, it seems like the blinded evaluator provided the most accurate evaluation of patient outcome, but I think if a good endpoint is developed -- and by good, I mean something that's really objective -- I would view that the treating investigator would equally provide accurate evaluation of that outcome.

In terms of the patient evaluation, if you have, like -- and again, this is not my area, but if you have, like, scales that measure quality of life in terms of the ease and the effectiveness, this is something that you may want to consider. But again, you know, I don't know if there are any scales that are validated, so that's going to be important, to look at validated scales.

Developing metrics, I don't know. I do mostly cancer research, so it will be nice if you can measure it, measure the lip at baseline and at follow-up and quantify that. I don't know how you can do this, if it's practical or not.

And the magnitude of change, I mean, I alluded to the greater than 1. If you think greater than 1 is clinically meaningful, it may be worth it

to establish that as your -- what's considered really a meaningful and a significant result of the patient. So that may be something that the Sponsor may want to validate in future trials.

DR. GALANDIUK: Mr. Melkerson.

MR. MELKERSON: Just to help the discussion, on Point (b), I think we're -- FDA is trying to get across is should it be investigator only, patient only, or both. And the example we put up there is actually, since it is objective both for the patient, what is optimal outcome, the question is should there actually be a requirement of both for future studies; in other words, in helping design the next set of products that are coming through, should it be both.

So I just want to make sure it came across that (b) is actually asking the question of is blinded investigator, treating investigator alone sufficient, or should there actually be a co-endpoint of both?

DR. GALANDIUK: Dr. Miller.

DR. MILLER: This is a very difficult question, and it gets at the core of how to do studies of esthetic surgery in general, even things like breast reconstruction. It's very hard to demonstrate the value of so many of these things because of the difficulty in defining endpoints.

But the way I like to think about this is, there are subjective endpoints and then there's objective ones. The subjective ones, you need as many of those as you can get and sort of synthesize them all together to

determine if the outcome, if you're getting an outcome. The treating investigator, he may look at the result, but his assessment of the result is actually affected by his remembrance of the preoperative result. And a person who is only seeing the postop result for the first time or even seeing two photographs, they're seeing a very limited amount of input to make their decision on, and the investigator may even be factoring in how happy the patient is. And that can sway him to thinking oh, that lip looks really good because the patient's so happy when objectively there may be no difference, you know, so this is the problem with it.

I think the subjective pieces are important. I think each of these people who you've -- I'm impressed with how thoroughly you thought this problem through and actually included the different people who'd have a legitimate say in the matter, the patient and these different investigators. But all that being said, it's very difficult to make any solid conclusions based upon that. That's why there must be objective measures. And I will repeat my disappointment.

Now, you did not follow through on some of the initial efforts. It sounds like you did, but you get digital, three-dimensional photographs and try to do measurements on these things, because in my opinion, if you can see a difference on a photograph, you can measure it somehow by an image analysis.

And I think that -- you can even do calculations of volume. You

don't have to see the entire volume of the lip. You can get, you know, a three-dimensional photo of that lip, and then you can calculate a best approximation of the -- lip and generate a volume. You can do these types of things. It takes some effort, it takes some commitment to the need for them. But I think that they're incredibly important for this whole area and I would encourage that to be pursued actively, so --

DR. GALANDIUK: Dr. Newburger.

DR. NEWBURGER: I agree with Dr. Miller, and I think that the blinded investigator is the one who has the greatest view with the least bias, but without having a baseline, it's really problematic. So it would have been really nice to have a 3-D image, at least, for those individuals to check at the baseline.

But we're talking about, I believe, what's going forward, and now that the technology is there, I think going forward, for other products, it's reasonable to request, in addition to these evaluations, also to have a 3-D assessment because it is certainly possible, not too difficult, to get the area under the curve with the 3-D imagining.

In terms of (b), I think patient satisfaction is very important in terms of safety and effectiveness and should be weighted equally. And I think that the 5 scale general device should be correlated with -- the 5 scale, the five-level scale, excuse me, could be correlated with a volumetric approach, in addition to the in vivo evaluators. And in terms of demonstrating the

magnitude of change, it may be that it's a very subtle change, so I don't know how to answer 6(d).

DR. GALANDIUK: Dr. Leitch.

DR. LEITCH: So I also think the blinded evaluator is a good tool and probably potential to be least biased, but also be effective in evaluating the independent photograph. Photographic reviewer probably suffers from what I did as a secondary photographic reviewer. Things didn't look so good to me.

But I do agree, also, that perhaps you could use photographic techniques if they were done differently to have a more objective determination of the benefit. And also, I think the patient thing is really important to evaluate the safety and effectiveness. I think that it certainly influenced me, you know, to look at those pictures and say, well, the patient thought that was great even if I don't, is -- you know, is -- that counts.

And I agree about just trying to get a more objective measurement that would -- I mean, I think even in the photos, perhaps, if you had a side view where you could see lip protrusion, that might also have been helpful.

And how might the Sponsor demonstrate the magnitude of the changed lip appearance? I think, again, this is a very subjective thing from the patient's perspective, how much lip fullness do they want, to them seems to be significant, so that will vary among patients as to what their final desire

is. So I suppose you have to kind of get an assessment of what that expectation is up front and, you know, was that met.

DR. GALANDIUK: Dr. Mount.

DR. MOUNT: This is impossible, trying to make something that is so subjective as beauty into a metric. Whether or not you have an evaluator, the evaluator's going to be biased, the treating physician's going to be biased just because everyone has kind of a different concept of what beauty is and particularly proportions and proportion of the lip.

So I think having as many evaluators as you have, I think it was a really great idea, and I think that getting that different viewpoint from all of them was very helpful even if sometimes they didn't correlate so well. I think that a bigger question in developing your metric is within your data, actually, which is the question, you know, would you do it again, because I'm still overwhelmed that so many people described their experience as disabling and they weren't able to function for a couple weeks and those are the same patients that came back for more.

Obviously, they are deriving a benefit, and I think that that's important to make sure that the person is happy with the result. It is really a unique area, but it's not also just a volumetric thing, and this is one thing that I have an issue with Dr. Miller. I mean, I think that we can get a really good 3-D volumetric assessment, but if it doesn't look appropriate, you know, like we can say oh, yeah it's plumped up 50%, but if it doesn't balance with the

rest of the face or other things like that, you know, maybe the bulk is in the wrong spot or it just makes a lip look strange, I think that that's unesthetic lips or in-esthetic lip.

So I think that you've done what you can. I think this is an impossible situation. I know that all the groups that do esthetic surgery are trying to find the ideal way of assessing beauty, and I just don't think that scientifically we can do that.

DR. GALANDIUK: Dr. Burke.

DR. BURKE: I think that, as we all said, beauty is subjective. But as far as assessor, I think that the blinded evaluator is the best, but I think the blinded evaluator should have the two photographs in front of him as does the independent photographic reviewer.

And I know in just looking a melanocytic lesions, when a patient comes in, I take pictures, again, of the lesion that I looked at before, but having the photograph with it shows very often a photograph is slightly lighter or slightly darker than the actual lesion. And I think if that blinded evaluator could have the photograph of the present condition in front of him at the same time he's looking at the pre-photograph, it would be a way to have, kind of, two assessments within one, and I think it really helps the blinded evaluator understand the first.

And I think that it's -- I just think it's very difficult for all of us physicians to remember the patient before, and I rely much more on my

pre-photograph than I do on my memory. And so that's my assessment of that.

I think, definitely, the patient evaluations are important, without a doubt. And I think that that was something very exciting to hear, in your results, that the patients, even when they had these transient adverse reactions, still were very happy with their correction and very often came back for more.

I think it's obviously very difficult to quantitate this, and I've done this a lot with small wrinkles for various, many various kinds of implants and -- but I do think you can quantitate something since you have the photographs. And if every patient had a lateral and the kind of photographs, you have the frontal photograph, if you just -- it's pretty easy to just trace the outlines to see the increase in depth from a lateral photograph and to see, which could be one quantitative measure and the difference in surface area from the frontal photograph.

And I think that, by doing -- I know that the technology may exist to do these volumetric measurements, but I think it's extremely difficult and extremely expensive and what the evaluator sees and the patient sees is much -- is very important, and to do something that high tech quantitative, even if it's possible, might not be worth it. But two photographs and tracing the photographs is something that's very easy and not expensive and quantitative, and I think it would be interesting to do that study just to see

what you find and if it works.

DR. GALANDIUK: Dr. McGrath.

DR. McGRATH: With regard to Question (a), for the future, I think all three prove fruitful. The blinded evaluator gives you the 3-D picture, the independent photographic reviewer can pick up the bruising and things like that, so I thought all three of those play together well.

For Part (b), I would say absolutely essential to have the patient involved since we know, from everything that we look at in esthetic surgery, that effectiveness equates with patient satisfaction and vice versa, whether we do elaborate scales and analyses or not, so that plays a key role.

I think the biggest opportunity is in Part (c), and I'm not sure it's for the FDA or for the next person coming along doing it, but I think for us clinicians doing this, this is our opportunity because right now, we're sort of at a global concept, you know, it's bigger so it's better.

But I think if we could start to really refine down the components in the lip and what we're accomplishing, really focus on what you gain with just working on the lip roll. In some patients you're probably spending a lot of time trying to get rid of the perioral wrinkles, so that's having an effect on your outcome.

And I think if we could start to pick out how much of, in the younger group and the older group, you're focusing on certain things like how much lip roll you want, how much perioral crease obliteration, how high you

want to go in terms of fullness, going into the upper lip above the vermilion, I think there's wonderful opportunities for our societies and for us to think about this and kind of refine this better so then we can come back with things that we can say are the real metrics for each of the two different groups that would tell us what makes the better lip, as well as the bigger lip.

And then as far as Part (d) goes, you know, you're asking, demonstrating the magnitude of change on an appearance scale. Again, I can't think of any enhanced technology that's going to do this, that's going to really demonstrate a change in effectiveness or clinical significance, so I don't really have an answer to Part (d).

DR. GALANDIUK: Ms. Brown.

MS. BROWN STRONG: I'll comment on the patient question.

My first thought was that you probably don't want the patient input because I think after a couple of weeks, the patient fails to see the difference between the initial lip and the enhanced lip. But then I realized that there are some issues, particularly if there are lumps inside the lip and stuff that you do want patient feedback on. But I actually think the best patient measure is when they have subsequent treatment. So I mean, to me, that say okay, obviously they were pleased.

I do want to say -- you know, I've thought about -- and I'm not a clinician, but I've thought a lot about the measuring of the volume, but I think the volume is not the important part but more the appearance of the volume,

which means the erasure of the lines. So that's my only comment on that.

DR. GALANDIUK: Ms. Mattivi.

MS. MATTIVI: I think maybe Steven Spielberg and DreamWorks should be brought into the equation here. They would probably be able to come up with some solution.

In terms of the assessor, in looking at the photographs, I had a big problem with not being able to see the whole face, and I don't know how the photographic review was done, whether they were able to see the patient's entire face. But that was a problem for me, and I think that was brought up, too. It's the idea of how these lips fit in with the rest of the proportions of the face that has more to do with the appearance than just the lips, themselves. Although, that being said, to be able to just focus in on that part probably helps to make it more objective, but I found that part difficult.

And as to the rest of it, patient evaluation, in my experience as a clinician, patients are often satisfied even with a suboptimum result because they like their treating physician or they like the clinician that they're working with. So I think that, at times, just introduces more noise.

And as to (c) and (d), again, I think Steven Spielberg would have the ideal solution for that.

DR. GALANDIUK: Mr. Halpin.

MR. HALPIN: From an industry perspective, my thoughts are that the -- when the blinded evaluator has the opportunity to look at the

baseline reading, that is probably the best efficacy measure for primary efficacy of a product, followed by live evaluation by the treating investigator then followed by IPR.

I think in this situation, we have an innovator trial where there may not be a comparative treatment, and therefore in order to protect the blinded evaluator, they remove some information, so I think we struggle with that in terms of how that happens, but there's no way to avoid that in a situation.

For patient evaluations, I think, you know, in looking at the pictures, you're looking at the lips and not the whole face, but the patient gets to look at themselves and draw an overall conclusion, so I think that's a really important additive factor. Maybe not a primary endpoint, but certainly a very important secondary endpoint.

And then for issues for (c) and (d), if you're thinking of how do you make this more quantitative, then my question would be how useful is that to people when they're actually using the product and reading the labeling? Does that help them or does a scale help them, and which one of those is the most effective way to do that? I think that would be very useful information.

DR. GALANDIUK: Mr. Melkerson, with regard to Question 6, it's a complicated one, we'll go over it step by step.

First, (a) which assessor, blinded evaluator, treating

investigator, or independent photographic reviewer, provides the most accurate evaluation of patient outcome, the -- I believe the majority of the Panel felt that the assessment was very subjective and that the more assessment tools you had, the better. The majority of the Panel, I feel, felt that the blinded evaluator was a very good tool, but in the data we were presented today was hampered by the fact that the blinded evaluator did not have the initial pre-treatment photos to look at.

There were, in terms of Question (b), what role should patient evaluations play in determining clinical safety and effectiveness, co-primary effectiveness endpoints, almost all the comments I heard were uniformly thinking that the patients' perception of effectiveness were very important and should play a part in future clinical trial design.

Regarding (c), what issues should a sponsor consider when developing a metric for evaluating effectiveness in lip augmentation, here there were very varied suggestions, everything from Dr. Miller, who suggested image analysis, photographic assessment of 3-D pictures, to several suggestions of portrait or profile photography in addition to the en face photography, other additions of quality of life metrics and emphasis on comparison to baseline, and then also defining discrete anatomic outcomes for assessment of improvement.

And (d), how might a sponsor demonstrate the magnitude of change on the lip appearance scale that correlates with a clinically significant

result, and again, there were numerous comments regarding what is a clinically significant result, and that would depend on the patient, and that that was very difficult to quantify. And, again, the comment made about defining discrete anatomic outcomes for different patients.

Is that satisfactory?

MR. MELKERSON: Thank you. I know you're trying to answer some very difficult questions, but this is aimed at future studies as much as this study.

DR. GALANDIUK: Okay. At this time, the Panel will hear summations, comments, or clarifications from the FDA. You have ten minutes.

DR. DURFOR: Thank you. I certainly won't need it.

I want to thank the Panel for their work outside this room and their work inside this room, for very thoughtfully considering this first-of-a-kind indication.

I wish also to just point one thing into focus, which is that our conversation here today is on the data that was in the PMA supplement. I know throughout this discussion we've heard about other uses of the product, sometimes in combination with -- mixed with anesthetics or things like that. That is a totally different product, it would be a combination product, the threshold for safety and effectiveness would be different, so I just want to remind you, as you go forward here, although either you have

heard or you have used the product in another way, our focus here today is simply on the data that we've brought before you.

Thank you again for your thoughtfulness.

DR. LAWRENCE: Yes. On behalf of Medicis, we also would like to thank the Panel for their very thoughtful and insightful discussions. It's very valuable to us, both for the study and also as we look at future indications, so again, I think we would just echo Dr. Durfor's comments on thanking you for your thoughtful comments and your deliberations.

DR. GALANDIUK: Thank you. Before we proceed to the vote, I would like to ask Ms. Mattivi, our Consumer Representative; Mr. Halpin, our Industry Representative; as well as Ms. Brown, our Patient Representative, if they have any additional comments to make.

MR. HALPIN: I just wanted to say that the study that we reviewed today I consider to be state of the art, and I think the FDA and the Sponsor did a really good job in putting together a study design where there were some unique situations, including lack of a comparator.

And I also was particularly struck by the functional test on the lip, which we really didn't talk about a lot today, but I thought those actually added a lot of value to this first-of-a-kind trial.

DR. GALANDIUK: Ms. Mattivi.

MS. MATTIVI: I would echo the same. I think, particularly in reviewing the material, something that is very subjective and esthetic in

nature, to have that functional component in there was very helpful and kind of helped give context and perspective to what we were asked to look at.

DR. GALANDIUK: And Ms. Brown.

MS. BROWN STRONG: I'll just say that I do appreciate the Sponsor's effort to bring this indication forward to provide better training for those who are using it and ultimately for the patients because I do think it would be beneficial for them.

DR. GALANDIUK: Dr. McGrath, did you have a comment?

DR. McGRATH: I was just going to comment that we never mentioned this, but the photography in the study was terrific. I can't imagine having better photography in terms of lighting and similarity of the pre- and postops over a six-month period. It really was quite impressive and as high a quality as you ever see in the very best journals, so thank you.

DR. GALANDIUK: Okay, we are now ready to vote on the Panel's recommendation to FDA for this PMA. The voting procedure has changed to an automated system. The Panel is expected to respond to three questions relating to safety, effectiveness, and risk versus benefit.

Ms. McCabe-Janicki will now read three definitions to assist in the pre-market approval application voting process. Ms. McCabe-Janicki will also read the indications statement for Restylane.

MS. McCABE-JANICKI: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical

Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert Advisory Panel on designated medical device pre-market approval applications (PMAs) that are filed with the Agency. The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

The definitions of safety, effectiveness, and valid scientific evidence are as follows:

Safety - 21 C.F.R. Section 860.7(d)(1) - There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness - 21 C.F.R. Section 860.7(e)(1) - There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid scientific evidence - 21 C.F.R. Section 860.7(c)(2) - Valid scientific evidence from well-controlled investigations, partially controlled

studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

The proposed indications for use statement for Restylane is:

Restylane is indicated for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds and for submucosal implantation for lip augmentation. Please discuss whether there is valid scientific evidence to support this statement. If not, please discuss possible changes to this statement and whether there is valid scientific evidence to support those changes.

I need to note here that I will be reading the Sponsor's proposed indication statement in its entirety as stated in the PMA supplement, which is the subject for today's Panel.

However, I want to note for the record that the Panel is being asked to vote only on the safety, effectiveness, and risk/benefit profile of the Sponsor's proposed new indication for Restylane, which is submucosal implantation for lip augmentation.

The following questions relate to the approvability of Restylane PMA Supplement P040024/s51. Please answer them based on your expertise, the information you reviewed in preparation for this meeting, and the information presented today. Your handheld remote will capture your vote after each question is read. We'll do a test question and then we'll go on to the three voting questions, and in each instance I'll ask you to press 1 to vote yes; 2 to vote no; and 3 to abstain.

Please be certain of your response before you select your answer as once the selection is made there will be no opportunity to change your vote. Before we begin, we'll take a test vote to verify that the voting remotes are working properly.

Here's the test question, so please -- oh, everybody -- okay, 1 for yes; 2 for no; 3 to abstain. As you vote, your name will disappear. Okay, all right. It's ready. Please press 1 to vote yes; 2 to vote no; and 3 to abstain. As you vote, your name will disappear from the screen. Yeah, please. Is it working?

Okay. Give it one more try. All right, yeah. We have paper ballots if we need them, but -- yeah. Okay, we're going to try one more time. Okay, try again. No. Okay, all right. Okay, in your folders you should have paper ballots. So if you could just take them out, write your name and your vote on each one: yes, no, or abstain. And then pass them to the center to me and just give us a minute to tally the votes. Thanks. And I'll go ahead and

read --

DR. GALANDIUK: Dr. Mount wanted a clarification.

MS. McCABE-JANICKI: Okay. And I will read the voting questions, just so we can have them on the screen.

DR. MOUNT: My clarification has to do with the age of the subject that we're approving this for. Are we approving this for all comers? The question doesn't indicate.

MR. MELKERSON: It's as the indication stated.

DR. MOUNT: It's all it covers, okay.

MS. McCABE-JANICKI: Okay, so just for the record, I'm going to go ahead and read the voting questions.

And Voting Question 1: Is there a reasonable assurance that Restylane is safe for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, and for submucosal implantation for lip augmentation? Your options are yes, no, or abstain.

Voting Question 2: Is there a reasonable assurance that Restylane is effective for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, and for submucosal implantation for lip augmentation? Yes, no, or abstain.

And Voting Question 3: Do the benefits of Restylane for mid-to-deep dermal implantation for the correction of moderate to severe facial

wrinkles and folds, such as nasolabial folds, and for submucosal implantation for lip augmentation outweigh the risks of Restylane for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, and for submucosal implantation for lip augmentation, for purposes of approval? Yes, no, or abstain.

And can I -- has everyone completed the vote? Yeah, okay. It's working now. Okay.

DR. GALANDIUK: Let's try the electronic voting one more time.

MS. McCABE-JANICKI: Okay. So we're going to start over.

Okay. Please vote on the test question. As you vote, your name should disappear from the screen. Okay. Dr. McGrath. Yes, okay.

Please go on to Voting Question 1. I'll read it.

Okay, Voting Question 1: Is there a reasonable assurance that Restylane is safe for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, and for submucosal implantation for lip augmentation?

Please vote yes -- 1 to vote yes; 2 to vote no; and 3 to abstain.

Such quick answers.

Okay, the poll is closed, and we'll move on to Voting Question 2. Okay. And I'll read it.

Is there a reasonable assurance that Restylane is effective for mid-to-deep dermal implantation for the correction of moderate to severe

facial wrinkles and folds, such as nasolabial folds, and for submucosal implantation for lip augmentation?

Please vote now. Press 1 to vote yes; 2 to vote no; and 3 to abstain.

Dr. Halabi, could you give yours a try? Yeah, great.

The votes are in and the poll is closed.

Voting Question 3: Do the benefits of Restylane for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, and for submucosal implantation for lip augmentation outweigh the risks of Restylane for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, and for submucosal implantation for lip augmentation, for purposes of approval?

Please vote now. Press 1 to vote yes; 2 to vote no; and 3 to abstain. Everyone has voted, and the poll is closed.

Okay, give us a moment to tally the votes, please. Oh, yeah. Okay, I'll read the votes into the record, and then we'll tally.

For Voting Question 1: Dr. Burke voted yes; Dr. Newburger voted yes; Dr. Miller voted yes; Dr. Mount abstained; Dr. Halabi voted yes; Dr. Leitch voted yes; Dr. McGrath voted yes.

Okay, for Voting Question 2: Dr. Burke voted yes; Dr. Newburger voted yes; Dr. Miller voted yes; Dr. Mount abstained;

Dr. Halabi voted yes; Dr. Leitch voted yes; Dr. McGrath voted yes.

And Voting Question 3: Dr. Burke voted yes; Dr. Newburger voted yes; Dr. Miller voted yes; Dr. Mount abstained; Dr. Halabi voted yes; Dr. Leitch voted yes; and Dr. McGrath voted yes.

Okay, so on all three voting questions, 1, 2, and 3, we had six votes for yes and one abstention. And that's for each, Voting Question 1, 2, and 3.

All right, voting question are now complete. If you would, just pass the voting devices towards me for collection.

DR. GALANDIUK: Okay. And I think we'll now ask the Panel members to discuss their votes, and I think we'll probably start with Dr. Mount first.

DR. MOUNT: I think I'm pretty easy to read. My only problem with voting completely yes -- I think it safe, I think it is effective. I don't think that the question was worded in such a way that I felt totally comfortable giving my final approval for safety, efficacy, and risk/benefit ratio to all populations, and it didn't specify for the pediatric population, and so that's the reason for my abstention.

DR. GALANDIUK: Can we go through the Panel and briefly comment on your votes and your thoughts?

Dr. Halabi.

DR. HALABI: I almost voted abstain for that same reason, but I

definitely believe that the benefits outweigh the risk and it's definitely effective and safe. And as such, I voted yes.

DR. GALANDIUK: Dr. Miller.

DR. MILLER: I think that the Sponsor did a nice job trying to objectively demonstrate that the effectiveness of this device, given the limitations of the tools we have to do that. And I'm very satisfied it's effective and that the risks outweigh -- or the benefits outweigh the risks.

DR. GALANDIUK: Dr. Newburger.

DR. NEWBURGER: I voted yes because this is a very challenging area to assess, but -- and it's already been done off-label for a very long time. I think that with the study design, I think it would, for the proposed population, I think that the safety and effectiveness were demonstrated. And I congratulate the Sponsor on having the persistence and the fortitude to carry this through. I know that many other companies have tried and failed.

DR. GALANDIUK: Dr. Leitch.

DR. LEITCH: I voted yes because I think the side effects appear to be short lived and not severe so that they don't prohibit doing something that is really elective for the majority of people to do. I think a lot of data was attempted in terms of trying to give objective data, as hard as that is to do, and taking into account the patients' comments as well. So I think it is sufficient for approval.

DR. GALANDIUK: Dr. Mount, one additional question to what

you said before with your abstention. Would restrictions on labeling or changes in the label format, would that have changed your vote?

DR. MOUNT: Yes. If it would've been specifically that it would be adults only, I would've voted yes on all accounts.

One thing that I would recommend and I don't know if I have the power or the authority or even the right to ask this, but as a pediatric provider, our population is very reticent to use things off label, and now that potentially this will be an on-label use for lip augmentation, you may see a lot more children that are being treated with this, and this is where I would very graciously recommend a post-market study, particularly on that population.

DR. GALANDIUK: Dr. Burke.

DR. BURKE: Well, certainly I want to congratulate the Sponsors. You provided excellent documentation, excellent evaluation of the safety and efficacy. And I think that having this indication for lip augmentation on-label will allow better training of physicians, of all physicians that will use the technique, and it will allow the possibility of more data collection for the subpopulations of interest. So I just think it's -- I'm very glad that it's now on-label.

DR. GALANDIUK: Dr. McGrath.

DR. McGRATH: Yes, I think we have voted the right outcome. Thank you. I have felt, from the beginning, that there were a couple of issues that I hope that the Sponsor will take into consideration as they go forward.

They've already indicated they will, and I would go back to two of them.

One, the concept of a staged implantation process to give you more control of the outcome rather than trying to do everything at once, the two-step or the touch-up idea to carry that forward.

And Number 2, to make serious efforts. We haven't gone back to really how to get our arms around this, but to capture the serious adverse effects.

I think there's something that I know this particular Sponsor has worked very closely with the professional societies on this. We saw some publications in meetings that have been going on. And I would hope that would go forward with a better definition of a good result in this particular instance so we don't have caricatures and odd things.

And I also think there's an opportunity here for each of you to take back to the professional organizations, possibly developing some guidelines on this for the teenage population, and I think working with the Sponsor, the organizations might want to move in that direction.

DR. GALANDIUK: I'd like to thank our distinguished Panel members, the FDA, the Sponsors for their presentation today.

Mr. Melkerson, do you have any concluding remarks?

MR. MELKERSON: First of all, Dr. Galandiuk, thank you for taking us through as Panel chair. I know this is -- you accepted last minute to fill in for us, so thank you very much.

I'd also like to thank the Sponsor and the Panel members for dealing with some very difficult questions that we posed to you, so thank you very much.

And I'd also like to thank the review team. And the one comment that was made about using functional assessments, I have to defer back to our clinician who helped review and posed that question.

DR. GALANDIUK: Okay. The April 27, 2011 meeting of the General and Plastic Surgery Devices Panel is now adjourned. Thank you.

(Whereupon, at 4:35 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

GENERAL AND PLASTIC SURGERY DEVICES PANEL

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Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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